

A 11C Raclopride PET Study of Dopamine
Activity, Pain Perception and Reward Processes
in Patients with Fibromyalgia

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Prof. Dr. Lutz Jäncke
Prof. Dr. Chantal Martin Sölch

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Summary

Findings suggest that pain and reward are mediated by similar neural pathways in the central nervous system (CNS) and that these pathways are related to both the dopamine (DA) and opioid system. While DA has well described roles in motivational states, reward processing and motor functions, a role for dopaminergic neurotransmission in modulating pain perception and natural analgesia has also been demonstrated. Striatal dopaminergic neurotransmission has been found to be altered in chronic pain syndromes such as burning mouth, atypical facial pain and Fibromyalgia syndrome (FMS).

FMS is a chronic, painful musculoskeletal disorder characterized by widespread pain, disturbed non restorative sleep, fatigue, and cognitive alterations and an increased incidence of depressive symptoms. The neuropathophysiology of FMS is still poorly understood. Based on the proposition that a disruption of normal dopaminergic neurotransmission may make a substantial contribution to the pathophysiology of FMS, the prevailing motive for this project was to investigate the modulation of pain perception by DA in FMS patients compared to healthy controls using the [^{11}C] raclopride Positron Emission Tomography (PET) method. Because chronic pain has been suggested to impair reward processing and because FMS is often associated with depression - a condition in which the neural processing of rewards has been shown to be disabled, we tested whether the dopaminergic responses to financial rewards were impaired in FMS and whether this impairment could differentiate between FMS patients with and without depression.

We investigated DA D2/D3 receptor availability at rest and subjective ratings of pain related to the administration of painful thermal stimulation in 17 healthy subjects, 13 subjects fulfilling the American College of Rheumatology (ACR) classification criteria for FMS without psychiatric comorbidity, and 11 subjects meeting the ACR criteria for FMS and the

criteria for major depressive disorder (MDD) (Report 1). Additionally, we measured the endogenous DA release associated with unpredictable monetary rewards during Bolus-plus-Infusion [^{11}C] raclopride PET scanning in the same population (Report 2).

Findings from report 1 surprisingly revealed no differences in striatal D2/D3 receptor availability between FMS patients with and without co-morbid MDD compared to healthy controls. Furthermore, different associations between D2/D3 receptor availability and pain perception were found between FMS patients and healthy subjects. Our results suggested that alterations in the dopaminergic system appear to be linked to pain sensitivity and secondly, that depression could influence pain perception in FMS patients.

Report 2 provided evidence for increased DA release to unpredictable monetary rewards in FMS patients compared to healthy controls which was more prominent in FMS patients with co-morbid depression. These results suggested dysfunctional DA responses to monetary rewards in FMS patients relative to healthy controls and that the dysfunctional reward circuitry could be associated with co-morbid depression in the pathology of FMS.

This work presents compelling evidence for alterations in the dopaminergic system as well as dysfunctional DA responses to monetary rewards in FMS. These findings provide further insight into the neuropathophysiology of FMS by addressing common neural bases of FMS and depression.

Zusammenfassung

Aktuelle Studienbefunde deuten auf eine ähnliche Verarbeitung von Schmerz und Belohnung durch neuronale Bahnen des Zentralen Nervensystems (ZNS), welche beide mit dem Dopamin- und dem Opiatsystem assoziiert sind. Gut dokumentiert ist eine Beteiligung dopaminerger Prozesse an der Verarbeitung von Belohnungsreizen.

Hinsichtlich einer Beteiligung von Dopamin (DA) an der Schmerzregulation gibt es ebenfalls einige Hinweise, wobei die genaue Rolle von DA bei der Schmerzwahrnehmung und Nachlassen von Schmerzen noch unzureichend geklärt ist. Einige empirische Befunde, deuten darauf hin, dass bei chronischen Schmerzpatienten, einschliesslich Patienten mit neuropathischen Schmerzen und Fibromyalgie Syndrom (FMS) eine Dysfunktion zentraler dopaminerger Funktionen vorliegt. FMS ist eine chronische schmerzhaft muskuloskelettale Erkrankung, die durch weitverbreitete Schmerzen, Hyperalgesie, Morgensteifigkeit und eine erhöhte Prävalenz depressiver Symptomatik gekennzeichnet ist. FMS ist unheilbar und bisher nur schwer zu behandeln. Über die neuropathologischen Grundlagen von FMS gibt es insgesamt noch viele Unklarheiten. Im Weiteren gibt es Hinweise für eine starke Komorbidität zwischen FMS und depressiven Störungen wobei oftmals Anhedonie, die reduzierte Fähigkeit angenehme Aktivitäten zu geniessen, ein Hauptmerkmal ist. Es wird vermutet, dass Anhedonie auf neurochemischer Ebene mit einer Unterfunktion des dopaminergen Systems in Zusammenhang mit der Verarbeitung von Belohnungsreizen korreliert ist.

Das Hauptziel dieses Projektes war es die modulierende Funktion von DA in Bezug auf Schmerzwahrnehmung mittels der [^{11}C] Raclopride PET Methode bei Patienten mit FMS zu untersuchen und mit einer gesunden Kontrollgruppe zu vergleichen. Ein weiteres Ziel bestand darin, zu testen, ob es zwischen FMS Patienten mit und ohne komorbide Depressionen Unterschiede in der DA Reaktion auf Belohnungsreize gibt, um ein besseres Verständnis

dafür zu erhalten, ob eine Änderung der neuronalen Reaktion auf Belohnung zur Bildung von komorbiden depressiven Symptomen in FMS beiträgt.

Wir untersuchten die Verfügbarkeit der Dopamin D2/D3 Rezeptoren und die subjektive Bewertung von thermal applizierten Schmerzreizen in 17 gesunden Probandinnen, 13 Fibromyalgiepatientinnen ohne psychiatrische Komorbidität, welche die Klassifikationskriterien für Fibromyalgie gemäss den Kriterien des American College of Rheumatology (ACR) erfüllten sowie 11 Frauen, welche die Fibromyalgiediagnose gemäss den ACR Kriterien sowie zusätzlich die Kriterien einer Majoren Depression (MDD) erfüllten (Artikel 1). Zusätzlich haben wir die endogene DA Ausschüttung in Bezug auf unvorhersehbare monetäre Belohnungsreize während Bolus-plus-Infusion [^{11}C] Raclopride PET Scanning in den gleichen Studienteilnehmern untersucht (Artikel 2).

Die Ergebnisse des 1. Artikels konnten überraschenderweise keinen Unterschied in der striatalen D2/D3 Rezeptorverfügbarkeit zwischen FMS Patienten mit und ohne komorbide Depressionen im Vergleich zu gesunden Kontrollen zeigen. Jedoch konnten unterschiedliche Assoziationen zwischen der D2/D3 Rezeptor Verfügbarkeit und der Schmerzwahrnehmung zwischen FMS Patientinnen und gesunden Kontrollen nachgewiesen werden. Unsere Ergebnisse deuten darauf hin, dass Änderungen im dopaminergen System mit der Schmerzwahrnehmung assoziiert sein könnten und dass komorbide Depressionen einen Einfluss auf die Schmerzwahrnehmung bei Fibromyalgie haben könnten.

Die Ergebnisse des 2. Artikels demonstrieren eine höhere Dopaminausschüttung als Reaktion auf unvorhersehbare monetäre Belohnungsreize bei FMS Patientinnen als bei gesunden Kontrollen. Die Dopaminausschüttung war bei FMS Patientinnen stärker ausgeprägt als bei gesunden Kontrollen und zwischen den beiden FMS Gruppen stärker ausgeprägt bei FMS Patientinnen mit komorbiden Depressionen als bei denjenigen Patientinnen ohne

Depressionen. Die Resultate des 2. Berichts belegen dysfunktionale DA Reaktionen in Bezug auf unvorhersehbare Belohnungsreize bei Fibromyalgiepatienten und deuten auf ein dysfunktionales Belohnungssystem, welches in Zusammenhang mit der Neuropathophysiologie von Fibromyalgie und den komorbiden Depression stehen könnte. Zusammengefasst präsentiert diese Arbeit eindeutige Hinweise für pathologische Änderungen im dopaminergen System im Zusammenhang mit der Schmerzwahrnehmung sowie Hinweise für dysfunktionale DA Reaktionen in Bezug auf monetäre Belohnungsreize bei Fibromyalgiepatienten. Diese Befunde geben weitere Einblicke in die Neuropathophysiologie von FMS durch den Untersuch der gemeinsamen neuronalen Grundlagen von Fibromyalgie und Depression.

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Original research articles included in this doctoral thesis***Report I*****Relation of Dopamine Receptor 2 Binding to Pain Perception in Female Fibromyalgia Patients with and without Depression – an [¹¹C] raclopride PET Study**

Ledermann K.^{1,2}, Jenewein J.¹, Sprott H.³, Hasler G.⁴, Schnyder U.¹, Warnock G.⁵, Johayem A.⁵, Kollias S.⁶, Buck A.⁵, Martin-Soelch C.^{1,2}

¹ University Hospital Zurich, Department of Psychiatry and Psychotherapy, Zurich, Switzerland

² University Fribourg, Department of Psychology, Division of Clinical and Health Psychology, Fribourg

³ Painclinic, Basel, Switzerland

⁴ University Bern, Psychiatric University Hospital, Bern, Switzerland

⁵ University Hospital Zurich, Department of Nuclear Medicine, Zurich, Switzerland

⁶ University Hospital Zurich, Department of Neuroradiology, Zurich

Report II**Increased Dopamine Release to Unpredictable Rewards in Female Fibromyalgia Patients with Comorbid Depression – a [¹¹C] Raclopride Bolus Plus Infusion PET Study**

Ledermann K.^{1,2}, Jenewein J.¹, Sprott H.³, Hasler G.⁴, Schnyder U.¹, Warnock G.⁵, Johayem A.⁵, Kollias S.⁶, Buck A.⁵, Martin-Soelch C.^{1,2}

¹ University Hospital Zurich, Department of Psychiatry and Psychotherapy, Zurich, Switzerland

² University Fribourg, Department of Psychology, Division of Clinical and Health Psychology, Fribourg

³ Painclinic, Basel, Switzerland

⁴ University Bern, Psychiatric University Hospital, Bern, Switzerland

⁵ University Hospital Zurich, Department of Nuclear Medicine, Zurich, Switzerland

⁶ University Hospital Zurich, Department of Neuroradiology, Zurich

Chapter 1

Outline of this thesis

This thesis is organized as follows: After a general introduction into the subject and aims of this thesis, theoretical background information is provided in chapter 2. First, some basic principles and properties of the human pain system are briefly outlined. Next, Fibromyalgia syndrome (FMS) is presented by reviewing important findings with a particular emphasis on altered pain modulation and pathogenesis of FMS. Next, the role of the basal ganglia in nociception and pain is described including findings supporting an implication of DA in pain and reward and alterations of pain-reward interactions with chronic pain. The empirical work is described in chapters 3 and 4. The first study, *Relation of Dopamine Receptor 2 Binding to Pain Perception in Female Fibromyalgia Patients with and without Depression – a [^{11}C] Raclopride PET Study*, is presented in Chapter 3 followed by the second study, *Increased Dopamine release to unpredictable Rewards in female Fibromyalgia patients with co-morbid depression – a [^{11}C] Raclopride Bolus plus Infusion PET study*, in Chapter 4. Chapter 5 provides a synopsis of this work and highlights the main limitations and conclusions that can be drawn from these studies.

General Introduction

To be in physical pain is to find yourself in a different realm- a state of being unlike any other, a magic mountain as far removed from the familiar world as a dreamscape. Usually pain subsides, one wakes from it as from a nightmare, trying to forget it as quickly as possible. But what of pain that persists? The longer it endures the more excruciating the exile becomes. Will you ever go home? You begin to wonder, home to your normal body, thoughts, life? (Melanie Thernstorm, 2010) ¹

¹ Melanie Thernstrom, *The Pain chronicles: Cures, Myths, Mysteries, Prayers, Diaries, Brain Scans, Healing and the Science of Suffering* (New York: Farrar, Straus and Giroux; 2010, p.3)

Chronic widespread pain has been described in the literature since the 19th century (Gamsa, 1994). During this time, the concept of fibromyalgia as a clinical entity we know today was probably unknown to most physicians. However, throughout history people have reported illnesses with strikingly similar symptoms. One prominent example is the great Mexican painter Frida Kahlo (1907-1954) who was without a doubt one of the most intense and emotive artists of the 20th century. After a car accident at the age of 18, she suffered severe, widespread pain and profound fatigue. Generalized pain and exhaustion accompanied her for the rest of her life. To explain Frida's chronic illness, Martinez-Lavin et al. (2000) suggested that she suffered posttraumatic fibromyalgia. A drawing in Frida's diary where she depicts herself in pain with 11 arrows pointing to anatomical sites near the conventional fibromyalgia tender points reinforces this diagnostic impression (Martinez-Lavin, Amigo, Coindreau, & Canoso, 2000). Fibromyalgia syndrome (FMS) is characterized by persistent widespread pain, stiffness and tenderness of the muscles, tendons and joints and by the presence of tender points in well-defined anatomical areas (Wolfe, 2010; Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, & Campell, 1990). Disturbed, non-restorative sleep, fatigue, and cognitive alterations, all symptoms inherent in chronic pain disorders, are often a prominent feature of the clinical picture of FMS. The etiology of FMS

remains unknown, but the exploration of the pathophysiology underlying FMS has become an exciting field of inquiry as research groups all around the world strive to improve their understanding of this mysterious disorder (Hauser et al., 2009).

Recent findings suggest that pain and reward are mediated by similar neural pathways in the central nervous system (CNS) involving a complex network of subcortical and prefrontal structures related to both the dopamine (DA) and the opioid systems that influence each other on a neurobiological and motivational level (Borsook et al., 2007; Kut et al., 2011; Leknes & Tracey, 2008). While DA has well described roles in motivational states, reward processing and motor functions (for review see Berridge, Robinson, & Aldridge, 2009; Salamone & Correa, 2012), a role for dopaminergic neurotransmission in modulating pain perception and natural analgesia has also been demonstrated (for review see Wood, 2008). Furthermore, striatal dopaminergic neurotransmission has been found to be altered in chronic pain syndromes including higher DA D2 receptor availability in patients with neuropathic pain and reduced presynaptic D2 receptor availability in patients with FMS (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003; Wood, Patterson, et al., 2007). However, the exact role of DA in anti-nociception, the action or process of blocking the detection of a painful stimulus by sensory neurons, and pain perception is still unknown.

Mood disturbances are reported to be common in patients with Fibromyalgia, with stated prevalence rates of depression ranging between 30 and 80% (Thieme, Turk, & Flor, 2004). Additionally, there is a large body of evidence showing that the DA system is impaired in major depressive disorder (MDD) and that the processing of rewarding information is affected in this condition (Martin-Soelch, 2009; Willner, 2000). Anhedonia, defined as markedly diminished interest or pleasure in all or almost all activities, is a hallmark of depression (Marbach & Lund, 1981; Stieglitz, 2000) and it has been suggested that anhedonia could be

related to a hypofunction of the DA system which could affect the neural processing of rewarding information (Willner, 2000). Therefore it has been hypothesized that these alterations of the cerebral reward system could contribute to the development of depression in chronic pain (Borsook et al., 2007). Furthermore, recent evidence suggests that pain, in particular long-term pain, might impair several aspects of reward processing (Becker, Gandhi, & Schweinhardt, 2012; Loggia et al., 2014) but none looked at the precise role of DA in this relation.

Based on the proposition that a disruption of normal dopaminergic neurotransmission may make a substantial contribution to the pathophysiology of FMS (Wood, 2008), the aim of this project was to investigate the relationship between DA and pain perception in FMS. Further, because chronic pain has been suggested to impair reward processing and because FMS is often associated with depression - a condition in which the neural processing of rewards has been shown to be disabled, we tested whether the dopaminergic responses to financial rewards were impaired in FMS and whether this impairment could differentiate between FMS patients with and without depression. Therefore, the prevailing motive for this project that was supported by the Swiss National Foundation (32003B_127629/1, PI Prof. Chantal Martin-Sölch) was to investigate the modulation of pain perception by DA in FMS patients compared to healthy controls using the [^{11}C] raclopride Positron Emission Tomography (PET) method. This method allows to directly and non-invasively monitor changes in synaptic DA concentrations (Dewey et al., 1993). A second aim was to investigate whether the DA response to rewarding stimuli could differentiate between FMS patients with and without comorbid depression in order to better understand the depressive symptoms often associated with FMS. We correlated, on the one hand, DA D2/D3 receptor availability at rest with subjective ratings of pain related to the administration of painful thermal stimulation in 17 healthy subjects, 13 subjects fulfilling the American College of Rheumatology (ACR)

classification criteria for FMS (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, & Campell, 1990) without psychiatric comorbidity, and 11 subjects meeting the ACR criteria for FMS and the criteria for major depressive disorder (MDD) (Stieglitz, 2000). We compared the discriminative capacity, i.e., the individual's capacity to discriminate between lower and higher pain intensities, and the response criterion, i.e. the subject's tendency to report pain during noxious stimulation due to psychological factors. Ratios of striatal region/cerebellum tissue radioactivity concentrations (SCR) were calculated as a measure of D2/D3 receptor availability (Report 1). On the other hand, we measured the endogenous DA release associated with unpredictable monetary rewards during Bolus-plus-Infusion [^{11}C]raclopride PET scanning in the same subjects (Report 2). Findings concerning basic DA D2 receptor availability and subjective ratings of pain related to administration of painful thermal stimulation are presented in Report 1. Results regarding endogenous DA release associated with unpredictable monetary rewards are provided in Report 2. Our results on the role of DA in pain perception and reward processes in FMS may have important clinical implications for subjects affected with FMS and may provide relevant information for future research on FMS.

Chapter 2

Theoretical background

2.1 The human pain system

2.1.1 What is chronic pain? – a definition

Pain is a complex, bio-psycho-social phenomenon that develops from the interaction of several neuroanatomical and neurochemical systems with several cognitive and affective processes (Garland, 2012). The established definition of pain according to the International Association for the Study of Pain (IASP) is: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Bonica, 1979, p. 250). Under normal physiological conditions, pain serves as a protective mechanism critical for survival (Julius & Basbaum, 2001). Not only do afferent sensory inputs alert the organism to potential danger and enact mechanisms to move away from harm, but in the event that pain is inflicted, endogenous analgesic systems may reduce pain sufficiently for the organism to escape (Sandkuhler, 1996). When the pain becomes chronic however, a pathological state exists that does not serve as a warning for further tissue damage and generally is of no obvious advantage to the organism’s survival (Stein, 2013).

Chronic pain in turn is defined as pain that is present for more than 6 months or pain that persists beyond the expected time for healing (Mersky, 1994). There is a long list of chronic clinical pain conditions related to different medical conditions including but not limited to arthritis, diabetes, migraine, fibromyalgia, cancer and previous trauma or injury (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006).

The International Association for the Study of Pain (IASP) (Mersky, 1994) classified pain according to specific characteristics: (1) region of the body involved (e.g., abdomen, lower limbs), (2) system whose dysfunction may be causing pain (e.g., nervous,

gastrointestinal), (3) duration and pattern of occurrence, (4) intensity and time since onset, (5) and etiology. Moreover, three classes of pain have been distinguished: (1) nociceptive pain, (2) inflammatory pain associated with tissue damage and the infiltration of immune cells, and (3) pathological pain which is a disease caused by damage to the nervous system (neuropathic pain) or by its abnormal function (dysfunctional pain, like in fibromyalgia, irritable bowel syndrome, tension type headache, etc.) (Woolf et al., 1998). In the following section, a brief overview of the physiological basis of pain will be provided without excessive detail or comprehensiveness despite being an area of expanding complexity.

2.1.2 Functional neuroanatomy and neurochemistry of pain

Basically, pain emerges in the periphery by hurting the cruciate ligaments during sports or by tripping on a hot plate, or even worse, as a side effect of a more severe disease like cancer or HIV. When noxious stimuli impinge on the body from external or internal sources, information regarding the damaging impact of these stimuli on bodily tissues is transduced through neural pathways and transmitted through the peripheral nervous system to the central and autonomic nervous system. This form of information processing is known as nociception (Garland, 2012). The nociceptive system is a self-contained sensory system comprising peripheral sensory fibers connected to multiple spinal tracts and brain regions. Pain stimuli are sensed by specialized nociceptors - a highly specialized subset of primary sensory neurons that respond only to pain stimuli (McCleskey & Gold, 1999). The resulting pain signal travels from the periphery to the spinal cord along an A δ - or C-fiber. Because the A δ -fiber is thicker than the C-fiber, and is thinly sheathed in an electrically insulating material (myelin), it carries its signal faster (5-30 m/s) than the unmyelinated C-fiber (0.5-2 m/s). These sensory fibers modulate pain sensations that innervate all body tissues in order to

respond to the most compelling dangers (e.g. heat, cold, mechanical pressure and chemical stimuli) (Willis, 1985). Perception of pain occurs when stimulation of nociceptors is intense enough to activate A δ -fibers resulting in a subjective experience of a sharp, prickling pain (Bishop, Landau, & Jones, 1958) - known as first pain. As stimulus intensity increases, C-fibers are recruited, and the individual experiences an intense, burning pain that continues after the cessation of the stimulus - known as second pain (Ochoa & Torebjork, 1989). Second pain is diffuse, prolonged and aversive and is the main component of pain associated with chronic medical conditions. The central pathways for processing nociceptive information start at the spinal cord. The A δ - and C-fibers enter the spinal cord and synapse on second order neurons in the substantia gelatinosa (laminae II and III of the dorsal horns of the spinal cord). Activation of nociceptors is modulated by inflammatory and biomolecular influences in the local extracellular environment (Loeser & Melzack, 1999). Subsequently, nociceptive projection neurons in the spinal cord transmit information via the spinothalamic tract - the largest tract receiving its input from the fibers of the contralateral dorsal horn - which provides nociceptive information to thalamic nuclei as well as to primary (SI) and secondary (SII) somatosensory cortices (Garland, 2012; Willis, 1985). From these nuclei, nociceptive information is relayed to various cortical and subcortical regions including the amygdala, hypothalamus, periaqueductal grey, basal ganglia, and regions of the cerebral cortex (for review see Willis, 1985). Moreover, the insula and anterior cingulate cortex are consistently activated when nociceptors are stimulated and activation in these regions is associated with the subjective experience of pain (Coghill et al., 1994; Ploghaus et al., 1999). SI and SII are cortical regions believed to be involved in sensory-discriminative aspects of pain as well as in the anticipation of painful stimuli (Fernandez & Turk, 1992). Neuroimaging studies have consistently demonstrated several brain areas as having a major role in pain processing, and together these brain areas are commonly referred to as the “pain matrix” (Brooks & Tracey,

2005; Kupers & Kehlet, 2006) (Figure 2). The neurochemistry of pain and central-peripheral pain modulation is extremely complex comprising chemicals such as peptides (e.g. bradykinin), neurotransmitters (e.g. serotonin, dopamine), lipids (e.g. prostaglandins), and neurotrophins (e.g. nerve growth factor) resulting in the excitation of nociceptors and transmission of afferent signals to the dorsal horn of the spinal cord (Garland, 2012). Nociceptive signal transduction up the spinothalamic tract results in an elevated release of norepinephrine from the locus coeruleus neurons projecting to the thalamus, which transmits nociceptive information to the somatosensory cortex, hypothalamus and hippocampus (Garland, 2012). Opioid receptors in the peripheral and CNS result in the inhibition of pain processing and analgesia when stimulated by opiates or endogenous opioids such as endorphin, enkephalin or dynorphin (Garland, 2012). The brain does not passively receive pain information from the body, but actively regulates sensory transmission by exerting influences on the spinal dorsal horn via descending projections from the medulla (Garland, 2012; Heinricher, Tavares, Leith, & Lumb, 2009; Yaksh, 1987). Taken together, the study of the neural mechanisms involved in the perception, transmission, representation, and regulation of pain has indeed uncovered a complex neural system that integrates painful information permitting the organism's adaptation to potential bodily injury or tissue damage (Rainville, Bushnell, & Duncan, 2001). A schematic displaying nociception, pain perception and the behavioral response to pain in the human nervous system is presented in the following (Figure 1).

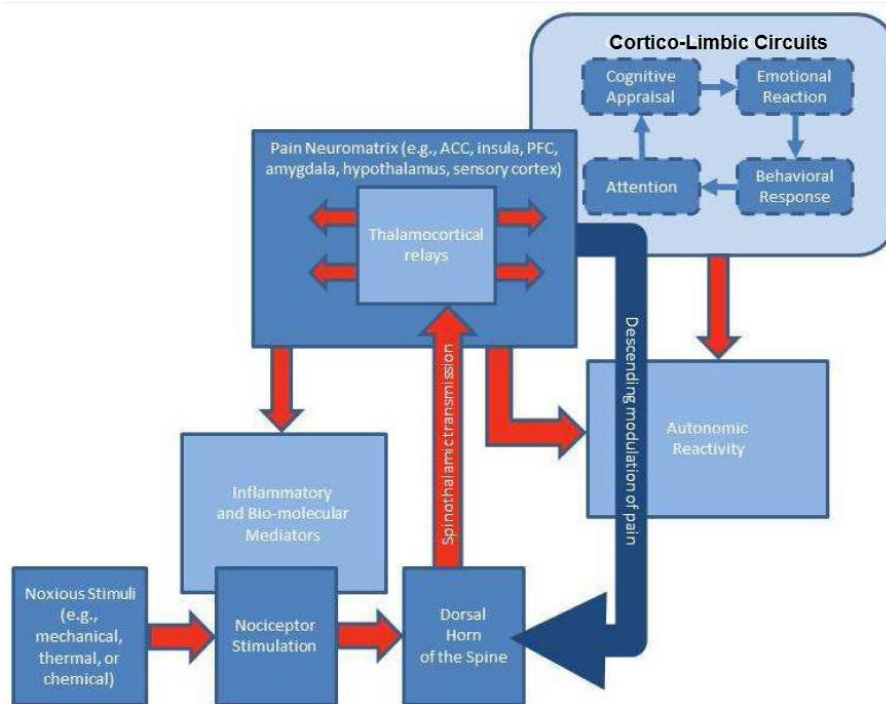


Figure 1. A schematic of nociception, pain perception and the behavioural response to pain in the human nervous system (adapted from Garland, 2012, p. 565). Additionally to the somatosensory elements described above, pain perception involves a number of psychological processes including attentional orientation to the painful sensation and its source, cognitive appraisal of the meaning of the sensation, and the subsequent emotional psychophysiological and behavioural reaction, which then feedback to influence pain perception.

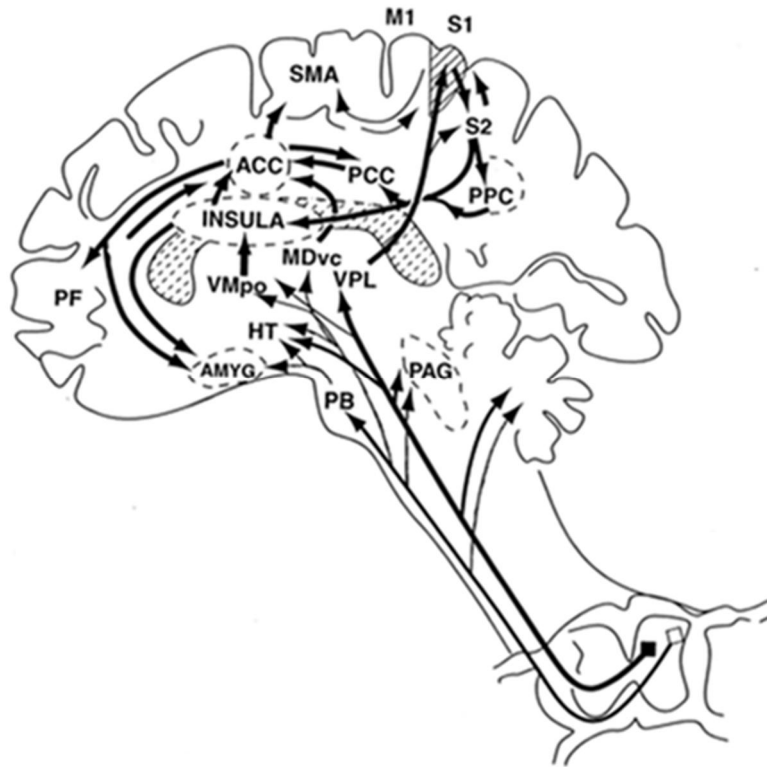


Figure 2. Schematic of ascending pathways, subcortical structures, and cerebral cortical structures involved in processing of pain. PAG, periaquaeductal gray; PB, parabrachial nucleus of the dorsolateral pons; VMpo, ventromedial part of the posterior nuclear complex; MDvc, ventrocaudal part of the medial dorsal nucleus; VPL, ventroposterior lateral nucleus; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; HT hypothalamus; S1 and S2 first and second somatosensory cortical areas; PPC, posterior parietal complex; SMA, supplementary motor area; AMYG, amygdala; PF, prefrontal cortex (adapted from Price, 2000, p. 1770).

2.1.3 Physiological basis of pain perception

Modern concepts of pain processing are based on the spinal gate control theory formulated by Melzack and Wall in 1965, which highlighted the modulation of incoming sensory information at the spinal level (Melzack & Wall, 1965). Prior to this, the prevailing view of pain processing was largely passive, consisting of a simple one-to-one relationship between nociceptive input and pain experience. Melzack and Wall (Melzack & Wall, 1965) suggested that the intensity and quality of pain were determined by both physiological and psychological variables. Their gate-control model proposed that the transmission of pain-related nerve impulses is modulated by a “gating” mechanism at the substantia gelatinosa (lamina II and III) of the dorsal horn of the spinal cord. This mechanism is influenced by the balance between large- and small-diameter nerve fiber activity, with small diameter fibers (A β -fibers) facilitating transmission (i.e. opening the gate) and large-diameter fibers (A δ - and C-fibers) inhibiting transmission (closing the gate). According to Melzack and Wall (Melzack & Wall, 1965), a central monitor must supervise the spinal output. If the output exceeds a certain level, the gate would open and a pain sensation would be created. Further, they postulated that modulation from cortical and subcortical structures acts upon the spinal gating mechanism. The central gray plays an important role in these descending inhibitory mechanisms, serving to close the gate. Subsequently, they extended the gate control theory by differentiating between sensory-discriminative, motivational-affective, and cognitive-evaluative aspects of pain. According to their extended model, sensory inputs are not the only determinants of pain. Moreover, these authors suggested that psychological and behavioral factors might have several routes of action in attenuating or enhancing pain perception. Even if some physiological assumptions of the gate-control theory were revised, the gate-control theory transformed the understanding of individual differences in the expression of pain. Psychological processes were no longer seen as mere reactions to pain, but as mediators in the

perception of pain. Factors influencing pain perception will be briefly mentioned in the next section.

2.1.4 Factors influencing pain perception

Perception of pain is influenced by various factors including cognition, emotion, mood, chemical or structural influences, context, genetics and central or peripheral sensitization (Tracey, 2010). Although nociception is usually the cause of pain, it is neither necessary nor sufficient and is very often not linearly related to the resulting pain (Tracey, 2010). This is because many factors influence nociceptive processing along the pathway from the nociceptor to the spinal cord and brain (Tracey & Mantyh, 2007). Pain perception involves several psychological processes, including attentional orienting to the painful sensation and its source, cognitive appraisal of the meaning of the sensation, and the subsequent emotional, psychophysical and behavioral reaction. Factors influencing pain perception are schematically described in Figure 3.

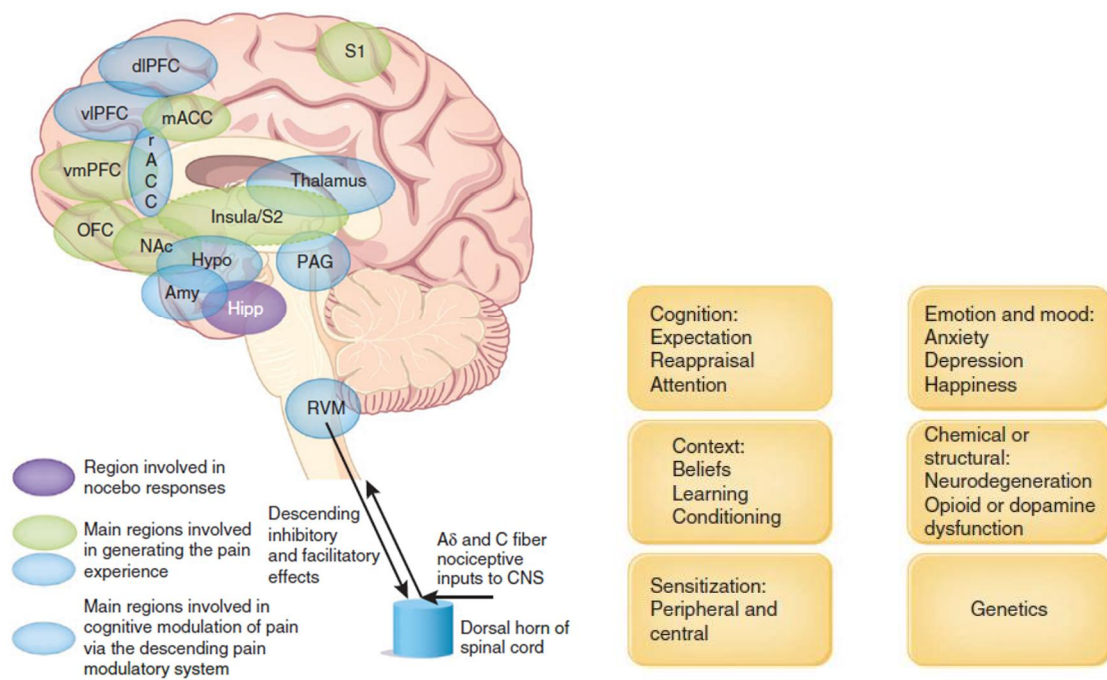


Figure 3. Schematic illustration of key brain regions involved in generating a pain experience and a description of the various factors that influence the pain experience listed in the text boxes. vmPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex; NAc, nucleus accumbens; Amy, amygdala; Hypo, hypothalamus; Hipp, Hippocampus; S2, secondary somatosensory cortex; S1, primary somatosensory cortex; dlPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; mACC, midanterior cingulate cortex (adapted from Tracey, 2010).

2.2. Current findings on the neuropathology of FMS

2.2.1 Definition and Classification

Fibromyalgia syndrome (FMS) is a disorder characterized by chronic widespread pain, joint stiffness and clinical symptoms that include cognitive and sleep disturbances and other abnormalities such as increased sensitivity to painful stimuli, increased sensitivity to multiple sensory modalities, and altered pain modulatory mechanisms and excessive symptom reporting (Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001; Wolfe, Ross, Anderson, Russell, & Hebert, 1995; Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, et al., 1990). Part of what makes FMS such a controversial disease is its diverse and complex list of symptoms. Patients with FMS are likely to have a history of headaches, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome and other functional gastrointestinal disorders, interstitial cystitis/painful bladder syndrome, endometriosis and other regional pain. Additional symptoms may include strange sensations on the skin (paresthesias), prolonged muscle spasms, nerve pain, muscle twitching, palpations and functional bowel disturbances (Silver & Wallace, 2002). FMS is also often associated with cognitive dysfunctions characterized by impaired concentration, problems with short- and long-term memory, short-term memory consolidation, cognitive overload and diminished attention span (Buskila & Cohen, 2007; Leavitt, Katz, Mills, & Heard, 2002).

According to the American College of Rheumatology (ACR) Criteria for the Classification of Fibromyalgia (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, et al., 1990), chronic widespread pain lasting at least three months in combination with mild or great tenderness at 11 or more of 18 specific tender points constitute the principal criteria for the diagnosis of FMS. Those classification criteria were primarily intended for research purposes and tender points were found to be the most

powerful discriminator, being able to separate FMS from other painful rheumatologic disorders. A tender point is defined as an anatomic site where an individual complains of pain when approximately 4kg of digital palpation is applied. The determined 18 tender point sites are illustrated in Figure 4. As these criteria alone do not encapsulate the complexities of FMS, Wolfe suggested in 2010 new ACR criteria (Wolfe, 2010) not requiring the presence of tenderness, but rather a list of several other symptoms including fatigue, unrefreshing sleep, and cognitive symptoms, as well as a mixture of other symptoms like headache, depression and lower abdominal pain/cramping. The hallmark symptom remains widespread pain, and a diagnosis of FMS requires this symptom. Because the defining symptom of FMS is widely distributed pain, it is usually considered a pain disorder, at least in the rheumatology communities. However, in other disciplines such as psychiatry, psychosomatic or general medicine, FMS is often considered to be a symptom or psychosomatic disorder (Kroenke, 2007). A recent study evaluating FMS symptoms in light of the Diagnostic and Statistical Manual-5 (DSM-5) criteria for Somatic Symptom Disorder (SSD) (American Psychiatric Association, 2013) found that FMS patients will satisfy criterion A for distressing somatic symptoms and criterion B that symptoms are “disproportionate” or excessive (Wolfe, Walitt, Katz, & Hauser, 2014).

In the following, the key features of the ACR classification criteria for FMS disease including the location of the nine paired tender points are presented.

2.2.2 Key features of the ACR 1990 classification criteria for Fibromyalgia

Table 1: Key features of the ACR 1990 classification criteria for Fibromyalgia (adapted and modified from Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, et al., 1990)

<i>Widespread pain</i>	Pain in the left/right side of the body, pain above/below the waist must be present. In addition, axial skeleton pain (cervical spine or anterior chest or thoracic spine or low back) must be present.
<i>Tender points</i>	Pain, on digital palpation (4kg/cm ²) applied over 4 seconds), must be present in at least 11 of the following 18 specified tender points bilateral sites; occiput, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteal, greater trochanter, and knee.
<i>Diagnosis</i>	Both above mentioned criteria must be satisfied. Widespread pain must be present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

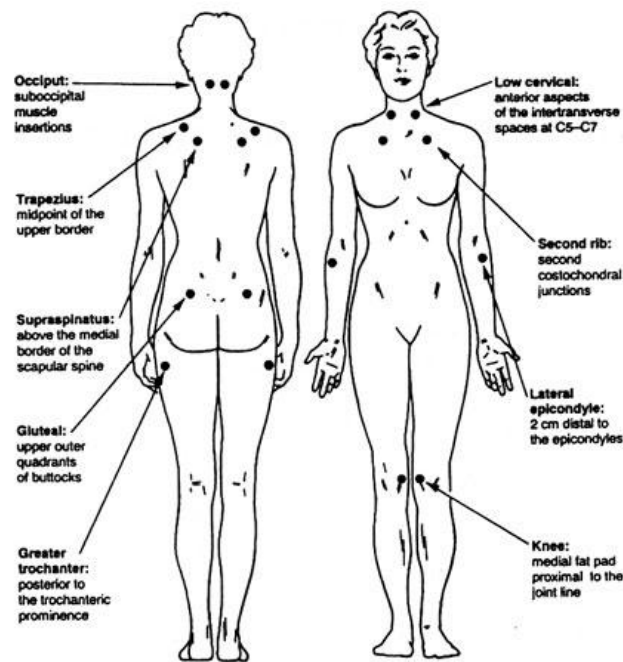


Figure 4. Location of the nine paired tender points that comprise the 1990 American College of Rheumatology criteria for fibromyalgia (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, et al., 1990).

2.2.3 Etiology of FMS

Depending on the classification criteria, FMS is estimated to affect 2-8% of the population (McBeth & Jones, 2007; Vincent et al., 2013; Wolfe et al., 1995) (3.4% for women and 0.5% for men) and is one of the most frequent diagnoses in rheumatologic practice (Vincent et al., 2013). It can develop at any age, including childhood, but most studies indicate an onset between the ages of 45-60 and indicate an increase in prevalence with age (Wolfe et al., 1995). The prevalence is similar in different countries, cultures and ethnic groups; there is no evidence that FMS has a higher prevalence in industrialized

countries and cultures (McBeth & Jones, 2007). Genetic factors may explain the strong familial predisposition to FMS and other chronic pain states (Arnold et al., 2004).

2.2.4 Comorbidities of FMS

Comorbidity of FMS and psychiatric conditions are frequent (Buskila & Cohen, 2007) including depression, panic disorders, anxiety and post-traumatic stress disorder (PTSD) (Buskila & Cohen, 2007). Depression is the most frequent psychiatric comorbidity in FMS (Fietta, Fietta, & Manganelli, 2007). Approximately 30% of patients with FMS have major depression at the time of diagnosis; the lifetime prevalence of depression is 74% compared to 60% for an anxiety disorder (Arnold et al., 2004; Giesecke et al., 2003). The high occurrence of depression in FMS has led to consideration of common neuroanatomical and pathophysiologic mechanisms of pain and depression which may explain the increased susceptibility to pain complaints in depression and the high incidence of depressive symptoms in FMS (Arnold et al., 2004).

2.2.5 Altered pain perception in FMS

In addition to the afore-mentioned characteristics of FMS, FMS patients show abnormalities in pain perception, including increased sensitivity to multiple types of painful stimuli, increased sensitivity to other sensory modalities, and alterations in pain modulatory mechanisms (Ceko, Bushnell, & Gracely, 2012). The following paragraph provides a short overview of the most important findings. Increased sensitivity to many types of painful stimulation has been reported in FMS. This includes pressure at non-tender point sites (Gracely, Petzke, Wolf, & Clauw, 2002), hot and cold pain (Berglund, Harju, Kosek, &

Lindblom, 2002; Desmeules et al., 2003; Lautenbacher, Rollman, & McCain, 1994; Petzke, Clauw, Ambrose, Khine, & Gracely, 2003), electrical stimulation and intramuscular hypertonic saline injection (Wood, Schweinhardt, et al., 2007). This hypersensitivity in FMS patients to painful stimuli has led some investigators to propose that FMS involves a hyper-vigilance to pain and pain-associated information (Asmundson, Kuperos, & Norton, 1997; Crombez, Eccleston, Van den Broeck, Goubert, & Van Houdenhove, 2004; Keogh, Ellery, Hunt, & Hannent, 2001). However, recent studies revealed that the hypersensitivity to unpleasant stimuli extends beyond the somatosensory pain system (Gonzalez et al., 2010; McDermid, Rollman, & McCain, 1996) giving rise to the hypothesis of a generalized hyper-vigilance to sensory stimuli in FMS (Gonzalez et al., 2010; Hollins et al., 2009; McDermid et al., 1996).

Aberrant pain processing, which can result in chronic pain, may be the result of several interconnecting mechanisms. A neural mechanism called central sensitization leads to an amplification of neural signaling within the CNS eliciting pain hypersensitivity which might explain why FMS patients present an expansion of the receptive fields of pain, along with hypersensitivity to touch (English, 2014; Yunus, 2007). This could explain why these patients would feel more pain than would be normally expected based on the degree of nociceptive input (English, 2014; Yunus, 2007). Another pathophysiological process that appears to be disturbed in FMS patients is the “wind-up” of central nociceptive processing of C-fiber input to the spinal cord (Ceko et al., 2012). The phenomenon of “wind-up” was introduced by Mendell and Wall (Mendell & Wall, 1965) and refers to the fact that repetitive electrical stimulation of C-fibers leads to an enhanced conduction of pain signals to the brain, resulting in a perceptual phenomenon of greater temporal summation of pain. Congruent with this observation, some FMS patients showed increased temporal summation of pain and

increased after-sensations at the termination of noxious stimulation (Staud, Vierck, Cannon, Mauderli, & Price, 2001).

Functional brain imaging studies support psychophysical findings of increased pain perception in FMS showing an augmentation of sensory processing throughout pain-related brain regions (Burgmer et al., 2009; Cook et al., 2004; Diers et al., 2008; Diers et al., 2011; Pujol et al., 2009; Staud, Craggs, Perlstein, Robinson, & Price, 2008). A number of anatomical imaging studies in FMS patients revealed decreased brain grey matter in regions associated with descending pain control circuitry and pain modulation (Schweinhardt, Sauro, & Bushnell, 2008; Villemure & Bushnell, 2009; Wiech, Ploner, & Tracey, 2008). Abnormalities in descending pain pathways comes from experimental testing of conditioned pain modulation (Julien, Goffaux, Arsenault, & Marchand, 2005) and neuroimaging studies demonstrating reduced connectivity of descending pain inhibitory networks (K. B. Jensen et al., 2012). Consistent with the idea that pain modulatory systems may be disturbed in FMS, FMS patients have shown abnormalities in neurochemical systems involved in pain control, including the DA system (Wood, Schweinhardt, et al., 2007) and the forebrain opioid system (Harris et al., 2007). The role of the DA system in pain perception in FMS will be discussed further in a separate section since the role of the DA system in FMS constitutes a central component of this thesis.

2.2.6 Pathogenesis of FMS

Controversy remains as to the cause and nature of FMS and the exact mechanisms of FMS pain remain to be determined. Several factors appear to be involved in the pathogenesis of FMS such as dysfunctions of the CNS and autonomic nervous systems, neurotransmitters, hormones, immune system, external stressors, psychiatric aspects and others seem to be

involved (for review see Bellato et al., 2012). The involvement of the brain and the CNS in the pathogenesis of this condition is supported by numerous functional neuroimaging studies (for review see Bellato et al., 2012). Descending inhibitory pain pathways also seem to be impaired in FMS, helping to exacerbate central sensitization (Staud et al., 2001; Watkins & Maier, 2005; Watkins, Milligan, & Maier, 2001). This reduced inhibition of pain in combination with the increased input of pain signals are considered the causes of hyperalgesia found in FMS (Woolf, 2011).

Specific neurotransmitters possibly involved in the pathogenesis of FMS have also been investigated. There is evidence for increases in the cerebrospinal-fluid (CSF), levels of Substance P, glutamate, nerve growth factor and brain-derived neurotrophic factor and low levels of serotonin, norepinephrine and DA - any of which could lead to inhibition of pain transmission and augmented pain and sensory processing (Alnigenis & Barland, 2001; Giovengo, Russell, & Larson, 1999; Hauser, Urrutia, Tort, Uceyler, & Walitt, 2013; T. S. Russell & Percy, 1994; Vaeroy, Helle, Forre, Kass, & Terenius, 1988; Wood & Holman, 2009). Abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system and immune system including reduced HPA activity with decreased cortisol production both at baseline and in response to a variety of stressors (Yunus, 2012), and flattened diurnal rhythm of the HPA axis (McLean et al., 2005) have been reported. As the HPA axis is closely linked with the autonomic nervous system, sympathetic hyperactivity as a component of the stress response that precipitates and perpetuates FMS symptoms has been identified (Staud, 2008). Additionally, enhanced inflammatory activity, shown by elevated serum levels of pro-inflammatory cytokines (e.g. $\text{TNF-}\alpha$, IL-1 and IL-6) have been demonstrated in FMS (Bazzichi et al., 2007; Salemi et al., 2003; Wang, Moser, Schiltewolf, & Buchner, 2008). Alterations in neuron-glial cell relationships have been found to be involved in the pathogenesis of chronic pain (Xie, Huo, & Tang, 2009) and are also suggested

to play a role in the genesis of FMS (Kadetoff, Lampa, Westman, Andersson, & Kosek, 2012). Taken together, the CNS has been investigated extensively while research on peripheral nervous involvement is less advanced (Blumenstiel et al., 2011) and an overall concept of the impact of the peripheral nervous system on pain in FMS is missing. Recent studies, however, function and morphology of small nerve fibers in patients with FMS were investigated by quantitative sensory testing, pain-related evoked potentials and quantified nerve-fiber density in skin punch biopsies, and compared with findings in patients with major depression and healthy controls. (Uceyler & Sommer, 2013). The observed neurophysiological and psychophysiological hypofunction was morphologically paralleled by reduction in dermal unmyelinated nerve-fiber bundles, whereas myelinated nerve fibers were spared, suggesting impaired small fiber function in FMS (Uceyler & Sommer, 2013). These findings point towards a possible neuropathic nature of FMS pain, and the authors argued that pain in FMS should be classified accordingly (Uceyler & Sommer, 2013).

2.2.7 Vulnerability factors for developing FMS

As FMS is frequently comorbid with mental disorders such as chronic fatigue syndrome, PTSD, irritable bowel syndrome and depression, FMS has been characterized as a “stress-related disorder” due to its onset and exacerbation of symptoms in the context of stressful events (Hudson, Goldenberg, Pope, Keck, & Schlesinger, 1992). Stress may therefore be an important precipitating factor in the development of FMS (Anderberg, Marteinsdottir, Theorell, & von Knorring, 2000). However, the risk of developing FMS symptoms is clearly affected by multiple factors. These include psychological distress (Ablin, Buskila, & Clauw, 2009; Robinson, McBeth, & Macfarlane, 2004), social factors such as socioeconomic status (Macfarlane, Norrie, Atherton, Power, & Jones, 2009), physical trauma

(Jones et al., 2011), genetic susceptibility and aberrant pain-processing mechanisms (Ablin et al., 2009; Clauw, 2009; Gupta et al., 2007). A systematic review reported significant associations between FMS and physical and sexual abuse in both childhood and adulthood (Hauser, Kosseva, Uceyler, Klose, & Sommer, 2011).

2.2.8 Treatment of FMS

FMS is best approached from a multidisciplinary perspective integrating pharmacological (in particular antidepressants and neuromodulating antiepileptics) and nonpharmacological treatment (importance of stress reduction, sleep, exercise) (Okifuji & Hare, 2013). Pharmacological therapies can be helpful in alleviating some symptoms, but patients rarely achieve meaningful improvements without adopting self-management strategies. Several classes of drugs have strong evidence for efficacy in treating FMS (Hauser, Petzke, & Sommer, 2010), including tricyclic compounds (amitriptyline, cyclobenzaprine; Arnold, 2007), gabapentinoids (Tzellos et al., 2010), serotonin and norepinephrine reuptake inhibitors (duloxetine; (Arnold et al., 2009), milnacipran (Geisser, Palmer, Gendreau, Wang, & Clauw, 2011)), and γ -hydroxybutyrate (I. J. Russell et al., 2011). Further, central neurostimulatory therapies are in development that presumably stimulate brain structures involved in pain processing showing promise for treating centralized pain states such as FMS (Hargrove et al., 2012).

2.3 Findings supporting the role of DA in pain and reward

2.3.1 The mesolimbic DA system

DA is a catecholamine neurotransmitter in the CNS described half a century ago (Carlsson, 1959). It is best known for its role in motor control, cognition and the neural processing underlying motivated and reward-related behavior (Kaasinen & Rinne, 2002; Nieoullon, 2002). Accordingly, the role of DA is evident in the neurobiology and symptoms of a myriad of neurological and psychiatric diseases, including Parkinson's disease, schizophrenia and addiction (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Bernheimer & Hornykiewicz, 1965; Di Chiara & Bassareo, 2007). The DA signaling across the brain involves several neuroanatomical pathways. One of them is the mesolimbic DA pathway comprised of neurons that project from the ventral tegmental area (VTA) of the midbrain to subcortical structures, such as the nucleus accumbens, thalamus, hippocampus, and amygdala (Le Moal & Simon, 1991).

Recent neuroimaging studies in healthy individuals have identified substantial overlap between the network of brain regions most commonly implicated in pain processing (Apkarian, Bushnell, Treede, & Zubieta, 2005) and regions that comprise the DA system (Leknes & Tracey, 2008). There are five subtypes of DA receptors, designated D1 through D5 (Sibley, Monsma, & Shen, 1993). D2 and D3 receptors are expressed throughout the brain with the highest concentration in the basal ganglia, globus pallidus, substantia nigra and ventral tegmental area (Gurevich & Joyce, 1999). D3 receptors are largely absent in the ventral tegmental area, but are expressed in the basal ganglia (most abundantly in the limbic striatum), substantia nigra, globus pallidus and in the anterior and medial thalamic nuclei (Suzuki, Hurd, Sokoloff, Schwartz, & Sedvall, 1998).

2.3.2 The role of the basal ganglia in nociception and pain

The basal ganglia comprise multiple subcortical nuclei at the base of the forebrain strongly interconnected with the cerebral cortex, thalamus and brainstem, as well as several other brain areas. They consist of the striatum (nucleus caudate, putamen and core of the nucleus accumbens), the external and internal segment of the globus pallidus, the subthalamic nucleus, and the substantia nigra (Graybiel, 2000, 2005) (see also Figure 5). The globus pallidus and substantia nigra can further be subdivided into smaller components that serve as output structures of the basal ganglia (Alexander & Crutcher, 1990). The main input area of the basal ganglia is the striatum, which receives synaptic input from cortical and subcortical afferents such as dopaminergic projections from the substantia nigra and the VTA (Alexander & Crutcher, 1990; Graybiel, 2000). The basal ganglia is associated with a variety of functions: including execution of motor, cognitive and emotional activities (Graybiel, 2004). Furthermore, preclinical studies support an involvement of the basal ganglia in pain processing. Although not exhaustive, these preclinical studies comprise electrophysiology (Bernard, Huang, & Besson, 1992; Chudler, 1998), analgesic effects of microinjections into these regions (Tashev, Belcheva, Milenov, & Belcheva, 2001), electrolytic lesion studies (Saade, Shbeir, Atweh, & Jabbur, 1996), chemical lesions of dopaminergic terminals (Saade, Atweh, Bahuth, & Jabbur, 1997; Takeda et al., 2005), activation of striatal dopamine system producing analgesia in rats (Lin, Wu, Chandra, & Tsay, 1981) and imaging drug effects in neuropathic rat models (Porro et al., 1999). Neuroimaging studies have added important information on basal ganglia activation in conditions of acute and chronic pain using a number of methods such as functional MRI (fMRI), pharmacological MRI, morphometric/anatomical measures (diffusion tensor imaging and gray matter volumetric analysis) and PET studies that allow whole brain evaluation of specific circuits (for review see Borsook, Upadhyay, Chudler, & Becerra, 2010). Activation in specific regions of the

basal ganglia (putamen, globus pallidus, caudate nucleus, nucleus accumbens) responding to noxious stimuli including thermal, mechanical, painful electrical and visceral pain have been reported in acute pain (for review see Borsook et al., 2010). Increased activation in the globus pallidus and putamen produced across multiple painful stimuli as well as a consistent decreased activity in the caudate nucleus to mechanical, cold and heat stimuli has been shown in chronic pain (Becerra, Harter, Gonzalez, & Borsook, 2006). Atrophy in a single cluster encompassing the right insula, the right ventromedial prefrontal cortex (vmPFC) and right nucleus accumbens has been shown in patients with complex regional pain syndrome (CPRS) (Geha et al., 2008) suggesting that chronic pain may alter basal ganglia structure. Additionally, findings suggest that basal ganglia loops integrate many aspects of pain including the integration of motor, emotional, autonomic and cognitive responses to pain and an analgesic role for dopaminergic neurotransmission within the basal ganglia in nociception and pain has been described (Chudler & Dong, 1995). Taken together, alterations in activation patterns and basal ganglia structure show an involvement of the basal ganglia in acute and chronic pain. In the following, an illustration of the basal ganglia is presented to demonstrate its placement in the human brain. The next section discusses the role for dopaminergic neurotransmission in the basal ganglia in nociception and pain.

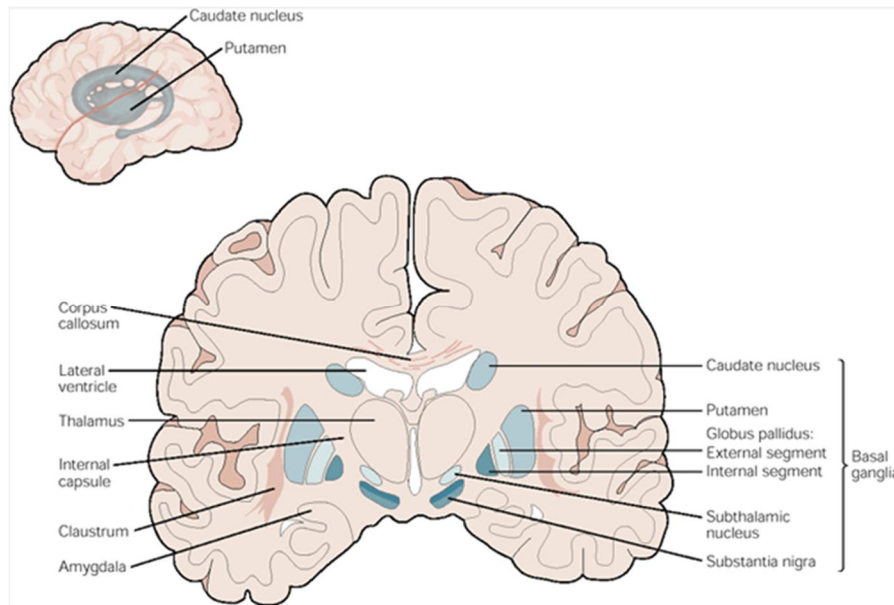


Figure 5. Illustration of the basal ganglia adapted from Nieuwenhuys et al. 1981 (Nieuwenhuys R, Voogd J van huiizen c the human central nervous system: A synopsis and Atlas. 2nd ed. Berlin Springer.).

2.3.3 The role of DA in pain and analgesia

Ample evidence from animal study models has highlighted how DA plays a critical role in anti-nociception. These rodent studies demonstrated that DA suppresses pain behaviors in response to phasic as well as tonic noxious stimuli of different modalities, including thermal, mechanical, and chemical stimuli (Lapirot et al., 2011; Magnusson & Fisher, 2000; Shimizu et al., 2004). This occurs primarily via activation of D2 (and likely D3) receptors in such areas as the basal ganglia, including the ventral striatum/nucleus accumbens, in the limbic cortex and the spinal cord (Shimizu et al., 2004). In humans, indirect evidence from genetic studies as well as studies in pain patients and patients with syndromes affecting central dopaminergic function (such as Parkinson's disease) supports a role of DA in the

processing of nociceptive stimuli (Brefel-Courbon et al., 2005; Jarcho, Mayer, Jiang, Feier, & London, 2012; Treister et al., 2009). Furthermore, analgesic properties of drugs which enhance DA neurotransmission such as for example Levodopa, an indirect dopaminergic agonist used to treat Parkinson's disease, reduces pain-related symptoms in patients with Parkinson's disease (Quinn, Koller, Lang, & Marsden, 1986), diabetic neuropathy (Ertas, Sagduyu, Arac, Uludag, & Ertekin, 1998) or herpes zoster (Kernbaum & Hauchecorne, 1981). Based on these lines of evidence, it has been hypothesized that DA has direct anti-nociceptive effects (Hagelberg et al., 2004; Jarcho et al., 2012; Wood, 2008).

Accordingly, recent neuroreceptor studies using PET to evaluate dopaminergic function have shed important insights on the role of DA in human pain experience. PET studies with [^{11}C] raclopride, a radiotracer that binds to D2-like DA receptors, have been used to assess tonic levels of striatal DA under baseline conditions, and phasic DA release associated with noxious stimulation. These studies revealed that healthy individuals with lower levels of tonic DA release in the striatum, indexed by higher levels of radiotracer binding under basal conditions, are more sensitive to noxious stimulation (Hagelberg et al., 2002). Additionally, the role of D2 receptors in pain modulation has been studied by Hagelberg et al. by determining the association between responses to experimental pain and D2 receptor binding potential at baseline (Hagelberg et al., 2004; Hagelberg et al., 2002). A significant negative correlation between cold pain threshold and D2 receptor binding potential in the right putamen has been reported. Cold pain tolerance was inversely correlated with DA D2 receptor binding potential in the right medial temporal cortex. Heat pain threshold had no significant correlation with D2 binding potential in any of the regions, but the elevation of heat pain threshold induced by conditioning cold pain was directly correlated with D2 receptor binding potential in the left putamen. A subsequent analysis compared subjects' cutaneous heat pain threshold baseline D2 receptor binding potential and likewise found an

inverse correlation between heat pain threshold and binding potential in the right putamen (Martikainen et al., 2005). No association could be determined between striatal DA binding potential and response to tactile stimulation, leading to the conclusion that the influence of striatal D2 receptors on sensory thresholds is selective for pain modality. Scott et al. examined the response of striatal DA in response to moderate sustained pain (i.e. hypertonic saline infusion into the masseter (Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006)). DA release was observed in the dorsal caudate nucleus and putamen quantitatively associated with individual variations in subjective sensory and affective ratings of pain. DA release in the nucleus accumbens was exclusively associated with variations in emotional responses. This study concluded that DA in the human basal ganglia is involved in response to pain and contributes to individual variations in physical and emotional pain experience. Furthermore, other PET studies with [^{11}C] raclopride have revealed that DA neurotransmission in the striatum increases during noxious stimulation, as indexed by decreased radiotracer binding (Scott et al., 2006; Scott, Stohler, Koeppe, & Zubieta, 2007). In summary, several studies have reported that DA D2/D3 receptors are involved in the regulation and perception of pain in humans (Hagelberg et al., 2002; Martikainen et al., 2005; Pertovaara et al., 2004; Scott et al., 2006; Wood, Schweinhardt, et al., 2007).

Evidence supporting the relationship between pain and function of the DA system in the brain is also derived from studies with chronic pain syndromes. Such studies have employed a variety of experimental techniques in groups of patients with different diagnoses (e.g., burning mouth syndrome, atypical facial pain, restless legs syndrome, FMS, complex regional pain syndrome (CRPS) or painful diabetic neuropathy (for review see Wood, 2008)). More precisely, in burning mouth syndrome, striatal dopaminergic function using 6- ^{18}F fluoro-L-DOPA PET found that these patients had significantly reduced fDOPA uptake in the right putamen with a non-significant decrease on the left. Further, these patients demonstrated

a significantly higher number of unoccupied D2 receptors in the left putamen with a lower D1/D2 receptor ratio in the bilateral putamen (Jaaskelainen, Forssell, & Tenovuo, 1997; Jaaskelainen et al., 2001). No difference in presynaptic DA synthesis or D1 receptor binding was observed in patients with atypical facial pain (Wood, Patterson, et al., 2007). However, these patients exhibited a non-significant tendency towards increased D2 receptor availability in the left putamen and a bilateral reduction in the D1/D2 ratio in the putamen. In summary, these findings demonstrate that patients with chronic pain conditions are associated with alterations in the striatal dopaminergic system characterized by reduced presynaptic activity of striatal DA neurons and changes in DA D2 receptor availability.

2.3.4 The role of DA in the pathophysiology of FMS

The first hint in the medical literature of a connection between FMS and DA was provided by Russell et al., who in 1992 reported lower concentrations of metabolites of DA, norepinephrine, and serotonin in the CSF of patients with FMS in comparison to healthy controls (I. J. Russell, Vaeroy, Javors, & Nyberg, 1992). Indirect pharmacological evidence of dopaminergic dysfunction in FMS was first provided by Malt et al. who reported that FMS patients had an augmented prolactin release in response to a single challenge dose of buspiron, a D2-Antagonist, in comparison with controls (Malt, Olafsson, Aakvaag, Lund, & Ursin, 2003) suggesting that FMS may be characterized by increased sensitivity or density of DA D2 receptors. The prolactin response to buspirone has been explained through dopamine antagonistic effect at the level of the pituitary gland (Meltzer, Simonovic, Fang, & Gudelsky, 1982).

Finally, studies using PET have provided direct evidence of a disruption in dopaminergic neurotransmission in patients with FMS. The first, using 6-[18F] fluoro-L-

DOPA to determine presynaptic DA activity of dopaminergic neurons, demonstrated a significant reduction in uptake in dopaminergic centers of the mid-brain (i.e. ventral tegmental area and substantia nigra) and in multiple regions of the pain neuromatrix wherein DA plays a role in natural analgesia, including the thalamus, insula, and cingulate cortex (Wood, Schweinhardt, et al., 2007). A subsequent study evaluated DA release associated with noxious stimulation in FMS patients in comparison with matched healthy controls. Tonic pain caused by the infusion of hypertonic saline resulted in DA release into the striatum in healthy females that correlated with subjective ratings of pain intensity (Wood, Schweinhardt, et al., 2007). In contrast, FMS patients demonstrated profound disruption of DA release with painful stimulation. Furthermore, these findings provide compelling evidence for the proposition that FMS could be associated with a disruption of dopaminergic neurotransmission. However the exact nature of this relationship and its role in FMS remains unclear.

2.3.5 The role of DA in the processing of reward information

Rewards can broadly be defined as desirable outcomes that serve to influence behavior and have been posited to serve various functions, such as inducing feelings of pleasure, eliciting exploratory or approach behavior, and increasing the frequency and intensity of behaviors that lead to rewards (Schultz, 2000). The identification of the brain's reward circuit can be traced back to the pioneering work of Olds and Milner (1954), who demonstrated that the placement of electrodes at particular areas of the brain in rats could elicit repetitive behavioral responses to trigger electrical stimulation. This seminal finding, which first mapped positive reinforcement to specific brain sites, initiated decades of research aimed at teasing apart the neural underpinnings of how a reward can shape an organism's behaviors or decisions. There is a large body of evidence that regions associated with the mesolimbic DA

pathway are involved in the neural processing of reward information in humans and in animals including the prefrontal cortex, striatum, VTA, ventral pallidum, hypothalamus, amygdala, and habenula (Haber & Knutson, 2010). Interconnected by transmitter systems involving DA, serotonin, glutamate, GABA and opioids have been incorporated into a conceptual “reward circuit” (Koob, Rassnick, Heinrichs, & Weiss, 1994). Reward processing is not a homogeneous entity and encompasses several regions and functions. Findings from neuroimaging studies indicate that the orbitofrontal cortex (OFC), amygdala and ventral striatum are implicated in reward prediction (Gottfried, O'Doherty, & Dolan, 2003). In this vein, it has been shown that the ventral striatum and amygdala responded to predictors of reward specifically, but not to reward itself after a learning process (O'Doherty, Deichmann, Critchley, & Dolan, 2002; Schultz, 2000). Learning of value predictions would take place in the ventral putamen and OFC through the activation of DA neurons facilitating the development of plasticity between sensory and reward representations in these regions (McClure, Berns, & Montague, 2003; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2011; Tremblay & Schultz, 1999). Finally, the striatum, specifically the dorsal part, might be implicated in stimulus-response learning as evidenced by activation of the dorsal striatum when there is a contingency between response and reward (Elliott, Newman, Longe, & William Deakin, 2004; Everitt et al., 2008; Volkow, Fowler, Wang, Swanson, & Telang, 2007). Rewards are also closely related to motivation defined by their capacities to trigger pleasant emotions to continue a behavior, by inducing subjective feelings of pleasure (O'Doherty, 2004). Reward may also act as positive reinforcement by increasing the frequency and intensity of behavior that leads to the acquisition of goal objects, as described in classical and instrumental conditioning procedures. Some studies investigated the direct implication of DA in response to rewards using the [^{11}C]raclopride PET method. As [^{11}C]raclopride binding is thought to reflect endogenous DA release, [^{11}C]raclopride binding

decreased in the ventral striatum in response to large monetary rewards compared with large monetary losses (Pappata et al., 2002). [^{11}C]raclopride binding has been shown to decrease in the putamen and caudate in response to unpredictable compared with predictable rewards (Zald et al., 2004) and in the ventral striatum (Martin-Soelch et al., 2011). In sum, these results point to an involvement of the mesocorticolimbic and mesostriatal DA systems in the processing of reward information. The following illustration provides an overview of reward structures in the human brain.

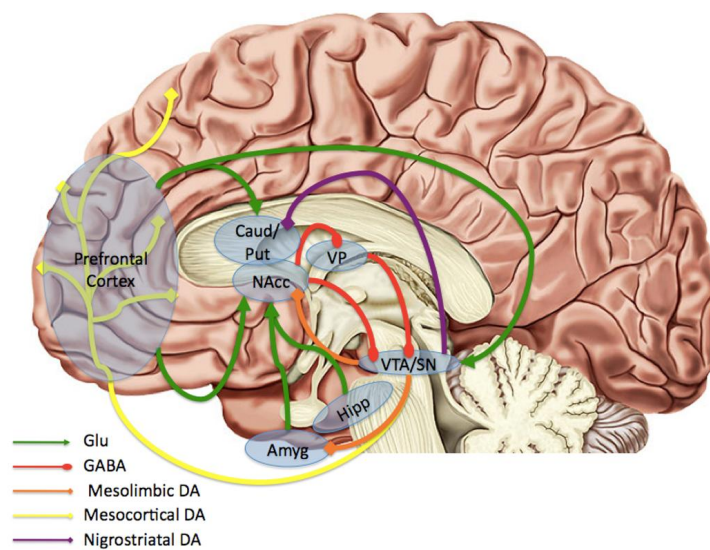


Figure 6. Schematic illustration of dopamine projection pathways and circuitry regulating DA release in the human brain. DA firing rates are maintained at tonic levels in part due to steady-state inhibitory firing from the ventral pallidum. Excitatory projections from prefrontal cortex project, amygdala and hippocampus synapse on striatal targets, including the nucleus accumbens. The nucleus accumbens sends GABAergic projections to the ventral pallidum, suppressing VP inhibition of VTA, thereby facilitating phasic burst-firing of VTA DA neurons. Note: Placement of structure labels is approximate. Amyg = amygdala; Caud = Caudate; DA = Dopamine; GABA = GABAergic projections; Glu = glutamatergic projections; Hipp = hippocampus; NAcc = nucleus accumbens; Put = Putamen; SN =

substantia nigra; VP = ventral pallidum; VTA = ventral tegmental area (adapted from Treadway & Zald, 2011).

2.3.6 Findings supporting the role of DA in pain and reward

Recent findings suggest that pain and reward are mediated by similar neural pathways in the CNS involving a complex network of subcortical and prefrontal structures related to both the DA and the opioid systems that influence each other on a neurobiological and motivational level (Borsook et al., 2007; Kut et al., 2011; Leknes & Tracey, 2008). In addition, several findings showed that rewards, including pleasurable stimuli such as food, music or odors, pleasurable activities and positive affective states have an analgesic effect and decrease perceived pain intensity (Leknes & Tracey, 2008; Lewkowski, Young, Ghosh, & Ditto, 2008; Roy, Piche, Chen, Peretz, & Rainville, 2009; Villemure & Bushnell, 2009). Relief fits the definition of reward and can be as pleasurable as other reward types (Leknes & Tracey, 2008). For instance, it has been shown that monetary gain and omission of monetary loss activated overlapping regions in the ventromedial prefrontal cortex (Kim, Shimojo, & O'Doherty, 2006; Ursu & Carter, 2005). Furthermore, activation in Nucleus accumbens has been shown to correlate with relief pleasantness during an appetitive reward task (Leknes, Lee, Berna, Andersson, & Tracey, 2011). In the context of pain and especially chronic pain, relief from pain is rewarding. A psychophysical study confirmed the rewarding qualities of pain relief (Leknes, Brooks, Wiech, & Tracey, 2008; Leknes et al., 2011). Neuroimaging studies yielded evidence for involvement of similar brain regions in pain relief and reward. For instance an involvement of the lateral prefrontal cortex has been shown in taste reward (Kringelbach, de Araujo, & Rolls, 2004) and also in hyperalgesic pain (Lorenz, Minoshima, & Casey, 2003). Further, fMRI and dopamine ligand PET studies showed involvement of the

nucleus accumbens and the ventral striatum in monetary reward (Scott, Stohler, Egnatuk, et al., 2007; Smith & Berridge, 2007) and drug reward (Drevets et al., 2001) and also in expectation of pain (J. Jensen et al., 2003; Scott et al., 2006) and pain-induced analgesia (Gear, Aley, & Levine, 1999). Additional anatomical substrates responsible for this mutual influence of pain and reward include the anterior and posterior insula, amygdala, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex (ACC), dorsal striatum, ventral pallidum, thalamus, hypothalamus midbrain, amygdala, hippocampus cerebellum and brainstem (for review see Leknes & Tracey, 2008).

2.3.7 Alterations of pain reward-interactions with chronic pain

Recent evidence suggests that pain, in particular long-term pain, impairs several aspects of reward processing. First, chronic pain is associated with anhedonia, i.e. the inability to feel pleasure (Marbach & Lund, 1981; Marbach, Richlin, & Lipton, 1983). Anhedonia has been hypothesized to be related to hypofunction of the DA system, that could affect the neural processing of rewarding information (Willner, 2000). Second, decreased reward sensitivity and/or decreased motivation has been observed in rats with neuropathic pain (Ozaki et al., 2002). Third, impaired operant learning of pain sensitization and habituation has been found in FMS patients (Becker, Kleinbohl, Baus, & Holzl, 2011). Fourth, impaired decision making based on reward and punishment has been reported in patients with chronic back pain and complex regional pain syndrome (CPRS) (Apkarian et al., 2004). Taken together, these findings suggest that pain-reward interactions are impaired by chronic pain. However, no other study has examined the precise role of DA in this relation so far. The following section contains the empirical work of this thesis.

3. Title: Relation of Dopamine Receptor 2 Binding to Pain Perception in Female Fibromyalgia Patients with and without Depression – an [¹¹C] raclopride PET-study

Ledermann K.^{1,2}, Jenewein J.¹, Sprott H.³, Hasler G.⁴, Schnyder U.¹, Warnock G.⁵, Johayem A.⁵, Kollias S.⁶, Buck A.⁵, Martin-Soelch C.^{1,2}

¹ University Hospital Zurich, Department of Psychiatry and Psychotherapy, Zurich, Switzerland

² University Fribourg, Department of Psychology, Division of Clinical and Health Psychology, Fribourg

³ Painclinic, Basel, Switzerland

⁴ University Bern, Psychiatric University Hospital, Bern, Switzerland

⁵ University Hospital Zurich, Department of Nuclear Medicine, Zurich, Switzerland

⁶ University Hospital Zurich, Department of Neuroradiology, Zurich, Switzerland

Corresponding author:

Katharina Ledermann

University Hospital Zurich

Department of Psychiatry and Psychotherapy

Haldenbachstrasse 16/18

8091 Zurich (Switzerland)

Katharina.ledermann@usz.ch

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Abstract

Dopamine D2/D3 receptor availability at rest and its association with individual pain perception was investigated using the [^{11}C] raclopride PET-method in 24 female Fibromyalgia (FMS) participants with (FMS+, N=11) and without (FMS-, N=13) comorbid depression and in 17 healthy women. Thermal pain thresholds (TPT) and pain responses were assessed outside the scanner. We compared the discriminative capacity, i.e. the individual's capacity to discriminate between lower and higher pain intensities and the response criterion, i.e. the subject's tendency to report pain during noxious stimulation due to psychological factors. Ratios of striatal region/cerebellum tissue radioactivity concentrations (SCR) were calculated as a measure of D2/3 receptor availability. The main findings were 1) no differences in striatal D2/3 receptor availability between FMS+ and FMS- patients compared to healthy controls; 2) a negative correlation between D2/3 receptor availability in the right caudate nucleus and TPT in FMS+; 3) positive associations between TPT and D2/3 receptor availability in left putamen, caudate and nucleus accumbens in healthy controls; 4) a positive association of the response criterion with D2/3 receptor availability in the right nucleus accumbens in FMS-; and 5) no correlations between D2/3 receptor availability and discriminative capacity in any region or group. Our results suggest that the dopaminergic function is associated with pain sensitivity in FMS patients in a different way than in healthy subjects, and that this association is mediated by psychological aspects of pain rather than by the discriminative capacity of the sensory system mediating pain.

Introduction

Fibromyalgia syndrome (FMS) is an idiopathic, diffuse soft-tissue pain syndrome with unclear pathophysiology (Bellato et al., 2012; Wolfe, 1990). Major depressive disorder (MDD) is the most frequent psychiatric comorbidity in FMS (Fietta et al., 2007). A growing awareness of the role of mesolimbic dopamine (DA) in pain perception, specifically in antinociception, has emerged in recent years (Hagelberg et al., 2004; Jarcho et al., 2012; Leknes & Tracey, 2008; Potvin, Grignon, & Marchand, 2009; Wood, 2008). Although its precise function in nociceptive processes is only partially understood, DA regulation has been shown to be disrupted in MDD and chronic pain (Epstein et al., 2006; Wood, 2008). Several Positron Emission Tomography (PET)- studies demonstrated altered post-synaptic striatal DA neurotransmission in chronic neuropathic pain syndromes including burning mouth, and atypical facial pain, (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003; Wood, Schweinhardt, et al., 2007) while an alteration of presynaptic DA transmission was evidenced in FMS. However, postsynaptic DA function has not been investigated so far in FMS and the role of depression in the DA changes observed in chronic pain is not clear.

Moreover a positive correlation between individual pain sensitivity and striatal baseline raclopride binding was observed in healthy volunteers (Hagelberg et al., 2002; Pertovaara et al., 2004; Scott et al., 2006). Pain sensitivity can be determined using the Signal Detection Theory (SDT) (Chapman, 1980; Clark, 1966), that distinguishes two measures: the discriminative capacity, a measure of neurosensory sensitivity, reflecting the subject's ability to discriminate between two stimuli of similar, yet distinct, intensities. A low discriminative capacity is associated with relative insensitivity to noxious stimulation and indicates an attenuation of neural activity in the sensory system (Clark & Mehl, 1971). The response criterion is independent from discriminability and locates the person's overall tendency to

report pain; a high value indicates a stoical attitude (Clark, 1974; Clark & Mehl, 1971). The response criterion and thermal pain threshold (TPT) were shown to be inversely correlated with the D2/D3 Binding Potential (BP) in the right putamen in healthy volunteers, whereas the sensory discriminative capacity was not significantly correlated with the D2/D3 BP in any striatal region (Pertovaara et al., 2004). The association between measures of pain sensitivity with D2/D3 binding has not been yet examined in chronic pain conditions.

Here, we investigated the D2/D3 receptor availability at rest between FMS participants with (FMS+) and without (FMS –) comorbid depression compared to healthy controls using the [^{11}C] raclopride PET method to measure postsynaptic striatal D2/D3 receptor availability. We expected FMS patients to show reduced [^{11}C] raclopride binding (measured as the ratio of striatum to cerebellum binding, SCR) in striatal regions compared to healthy controls, reflecting a decreased postsynaptic availability of D2/D3 receptors in these patients as already described at the presynaptic levels (Wood, Patterson, et al., 2007) and in agreement with findings for neuropathic pain conditions (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003). We expected the reduction to be more pronounced in FMS+ patients than FMS- patients. Additionally, we aimed to test the association between pain sensitivity and striatal D2/D3 receptor binding with regard to the role of comorbid MDD. We expected FMS patients to have decreased thermal pain thresholds (TPT) and thermal pain tolerance (TOL), correlated to altered D2/D3 receptor availability, but for pain responses to show no correlation with SCR in striatal regions. Together, we believe that such evidence would indicate that the dopaminergic influence on pain sensitivity is impaired in FMS.

Material and Methods

Subjects

Given the predominance of women in FMS (Wolfe et al., 1995) and to reduce the heterogeneity of study samples, we decided to only include women in this study. A total of 24 female FMS patients were compared to 17 age- and gender-matched healthy control subjects. Among the FMS patients 11 subjects were diagnosed with comorbid MDD. All FMS+ patients had the onset of MDD subsequent to the FMS diagnosis. A description of clinical and demographic data parameters for the FMS patients is provided in Table 1. FMS patients fulfilling the American College of Rheumatology (ACR) classification criteria for Fibromyalgia (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, et al., 1990) with decreased pressure pain thresholds at a minimum of 11 of 18 specific tender points, located in 9 paired regions of the body, were recruited from the Division of Rheumatology at the University Hospital Zurich. They were recruited through flyers in medical practices, advertisements in newspapers, and advertisements on websites associated with FMS. Controls were recruited through flyers on bulletin boards in public places. Current and/or chronic medical conditions, current and/or lifetime psychiatric diagnoses, acute or chronic pain and medication other than oral contraceptives were exclusion criteria for the controls. All FMS patients had their FMS diagnosis confirmed by an experienced rheumatologist (HS) through clinical examination, including measurements of pain thresholds at tender points using a digital dolorimeter (LD 100 NRS, AC Engineering Basel, Switzerland). FMS subjects had a mean pain duration of 13.46 years (SD=11.98), and a mean number of 16 tender points (SD=3.66). FMS subjects were allowed to continue their SSRI (selective serotonin-reuptake inhibitors), TCA (tricyclic antidepressants) and NSAID (non-steroidal anti-inflammatory drugs) medication during the study. A total number of 12 FMS patients were taking antidepressant medication either for

pain or depressive symptoms. The use of opioids, neuroleptics, antiepileptics, and lithium was an exclusion criterion. All subjects were tested for comorbid psychiatric disorders using the SCID (Structured Clinical Interview for DSM-IV (First, 2002)). This instrument was also used to diagnose MDD in the FMS group. The severity of depression was measured with the Beck Depression Inventory (BDI) (Beck et al., 1961), German version (Hautzinger, Bailer, Worall, & Keller, 1995), and the Montgomery Åsberg Depression Scale (MADRS) (Montgomery & Asberg, 1979). Anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (Laux, Glanzmann, Schaffner, & Spielberger, 1981). All participants were screened for general MRI and PET exclusion criteria, pregnancy (pregnancy test on the day of scanning), and breast-feeding. They were required to sign an informed consent which explained the procedures of the study prior to information and testing. The study was approved by the Ethical Committee of the Canton Zurich and the Swiss Federal Department of Health (Bagatzounis, Willner, Oppitz, & Flentje) in accordance with the current version of the declaration of Helsinki (Rickham, 1964) and the Swiss regulatory requirements.

PET image acquisition

[¹¹C] raclopride is an established in vivo method for estimating the availability of D2/D3 receptors in the brain. The D2/D3 receptor antagonist [¹¹C] raclopride was produced on site according to Good Manufacturing Practice (GMP) guidelines. PET scans were acquired using a PET/CT scanner with an axial field of view of 15.3 cm in 3D mode (Discovery STE, GE Healthcare, Waukesha, WI, USA) at the Department of Nuclear Medicine at the University Hospital Zurich. PET data were reconstructed using filtered back projection and segmented attenuation correction, for which a low dose CT scan was acquired.

On the day of the PET study, subjects were asked to eat a well-balanced meal before the PET scanning and not to consume too many liquids to ensure personal comfort during the scans. The PET measurement took place in the same time frame (Monday afternoon from 3 pm to 5pm) for all participants. [^{11}C] raclopride was injected as a slow bolus (260 \pm 20 MBq). Dynamic scanning was initiated at the time of tracer injection and continued for 60 min (31 frames of 4x15sec, 8x30sec, 9x60sec, 2x180sec, 8x300sec, total 60 min duration). Image data from 40-50 minutes were averaged and exported for further processing in the PMOD software (Version 3.2, PMOD Technologies, Zurich, Switzerland).

Magnetic resonance imaging

Each subject received a high-resolution T1 weighted magnetic resonance scan (3D fast-field echo scans with 160 slices, 1mm isotropic resolution, TR= 18ms, TE= 10ms, flip angle= 30°) for co-registration with PET images. All images were checked for structural abnormalities and lesions by a clinical neuroradiologist.

Determination of thermal pain threshold (TPT), pain tolerance threshold (TOL), and pain modulation

Standardized pain testing procedures were conducted by the same investigator on the same day as the PET scanning with each subject in a separate session in a quiet room with constant ambient temperature. Thermal pain threshold (TPT) and thermal pain tolerance (TOL) were determined using a method of limits procedure (Hansen, Hopf, & Treede, 1996). Thermal cutaneous pain response was measured by delivering heat stimuli to the thenar of the non-dominant hand with a 27-mm-diameter thermal contact thermode (CHEPS, Medoc Ltd,

Ramat Yishai, Israel). The CHEPS thermode has a heating rate of 70°C/s and a cooling rate of 40°C/s. The same heating and cooling rate was applied during the whole procedure. The CHEPS thermode has a subject response device that immediately records the temperature once activated, and resets the thermode to the adaptation temperature in preparation for the next trial. The area of the stimulus surface was 5.7. cm². TPT and TOL estimation was based on five thermal stimuli starting at 32°C and rising linearly at a rate of 1°C/s until it was stopped either by a button press or when the maximum temperature of 52°C was reached. To determine TPT, subjects were asked to press the button on the response device when they experienced pain for the first time. To examine TOL, subjects were asked to push the response button when the sensation on their hand became intolerable or unbearable. The experimental paradigm for the pain modulation was adapted and slightly modified from the study of (Pertovaara et al., 2004). Heat stimulation started at 34.5°C and the temperature was increased linearly at a rate of 3°C/s to one of the six predetermined temperatures (45.8, 46.3, 46.8, 47.3, 47.8, and 48.3°C) for a duration of 4s, after which the stimulus temperature returned to baseline. The interval between successive stimulations was 15s. Each stimulus temperature was applied eight times and the order the stimuli were presented was randomized across subjects. After presentation of each stimulus, the subject was asked to rate the sensation evoked by the stimulus using a numerical rating scale ranging from 0 = no pain at all to 10 = strongest pain imaginable. Before the actual testing sessions all subjects went through a brief training session in which they were introduced to the experimental condition. The area of stimulation was slightly varied by moving the thermode either to the left or right side for each trial to prevent sensitization.

Determination of the subject's discriminative capacity and response criterion

We chose the same components as (Pertovaara et al., 2004) derived from the Signal Detection Theory (SDT) to determine the individual response characteristics to pain. Discriminative Capacity was computed by the trapezoidal rule as the area below the Receiver Operating Characteristics (ROC) Curve which is generated by cumulating probabilities of hits and false alarms for each response elicited by the stimulus temperatures of 46.8° vs. 47.3° using PASW Statistics 21.0 (SPSS Inc., Chicago, Ill, USA). The exact description of the calculations of the response criterion is provided in detail elsewhere (Pertovaara et al., 2004). Briefly, the criterion was defined as the rating scale criterion where half the responses (to both stimulus intensities in each pair) are divided into higher response categories and the other half into lower response categories. The response criterion was defined as $C=0.5(Z_{SN}+Z_N)$. Within the calculation, the probability of rating a stimulus of 47.3° as painful (rating categories 6-10 pooled together) was converted to a Z score (Z_{SN}) as described by Gescheider (1997, pp.122-123 and Table A). The probability of rating a stimulus of 46.8° as non-painful (rating categories 1-5 pooled together) was also converted to a Z score (Z_N).

Data analysis*ROI analysis*

All PET emission scans were reconstructed using 3D filtered back projection including a 6mm FWHM Hanning filter, producing an estimated final FWHM (full width at half maximum) of 10-12mm. Corrections for subject motion during the 60 min PET acquisition were performed with a mutual information registration of each image frame to a standard frame (0-8min after injection) before attenuation correction. Based on the calculated motion, the transmission images were re-sliced and projected for final attenuation correction,

reconstruction and realignment. The realigned frames were summed to generate an image that was co-registered with the corresponding MRI image using PMOD software Version 3.2 (PMOD Technologies Ltd, Zurich, Switzerland). This was performed for the first 8 minutes of scanning, during which the radiotracer distribution was most sensitive to cerebral blood flow (CBF), and thus for the cortical outlines to be sufficiently evident in order to guide image co-registration. The PET frames were summed and co-registered with the corresponding magnetic resonance image, and both images were transformed linearly into standardized stereotaxic space using the Montreal Neurological Institute template (Collins, Neelin, Peters, & Evans, 1994). Mean tissue radioactivity concentrations were extracted using MRI based regions of interest (ROI's), defined on a template MRI image using PMOD software in the anteroventral striatum, putamen, nucleus accumbens, caudate nucleus and cerebellum after Drevets et al. (Drevets et al., 2001; Drevets et al., 1999). Each individual MRI was registered to the template brain and the ROI's were repositioned as needed to accommodate for individual differences in anatomy. The anatomical accuracy and symmetry of each set of individual ROI's was verified by a neuroscientist familiar with striatal anatomy (CMS). These ROI's were then back-transformed into the subject's native MRI space and applied to the co-registered PET images (example in Figure 1). Ratios of striatal region/cerebellum tissue radioactivity concentrations (SCR) were obtained. For each region, the ROI ratios for patients and controls were compared with those for FMS+ and FMS- patients and controls and correlated with pain thresholds and measurements.

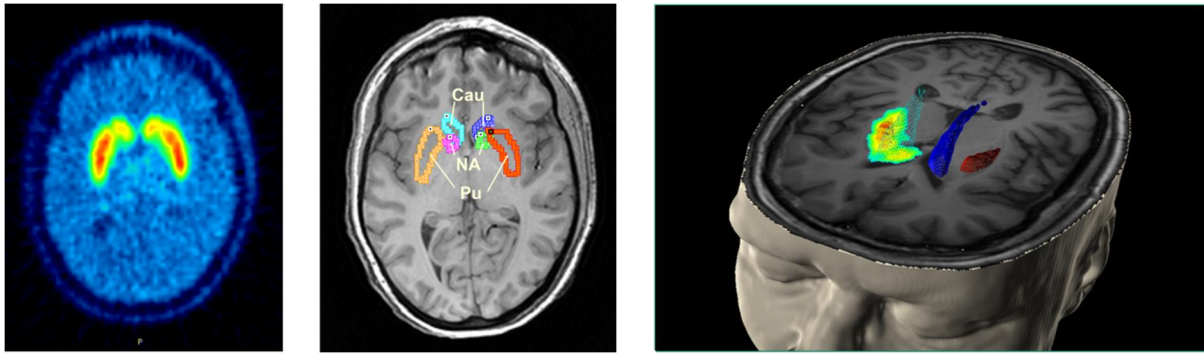


Figure 7: ROI's placement. Transverse view Cau: Nucleus caudatus; NA: Nucleus accumbens; Pu: Putamen

Analysis of behavioral data

PASW Statistics 21.0 software (SPSS Inc., Chicago, Ill, USA) was used for statistical analysis. Data distribution was tested with the Kolmogorov-Smirnov test and by observing data histograms. The results of normally distributed data are presented as mean \pm standard deviations. One way analysis of variance (ANOVA) was used to assess differences in D2/D3 receptor availability between groups (healthy, FMS-, FMS+) for each region of interest. The difference between groups for experimental pain ratings (pain threshold, discriminative capacity, and response criterion) of each group was tested using independent samples t-tests and one-way ANOVA followed by post-hoc tests, where appropriate. $P < 0.05$ was considered to represent a statistically significant difference.

Associations between D2/D3 receptor availability and psychophysical results (pain threshold, discriminative capacity, response criterion) were determined using Pearson's coefficient of correlation. $P < 0.05$ was considered as statistically significant.

Results

ROI Analyses

Mean SCR are summarized in Table 2. Analysis of postsynaptic D2/D3 receptor availability, measured by [^{11}C] raclopride, demonstrated no significant group difference between healthy subjects, FMS- and FMS+ patients in any of the striatal regions investigated (see Table 2). Analysis of postsynaptic D2/D3 receptor availability for the collapsed FMS group showed no group difference compared to healthy subjects.

Experimental pain ratings (thermal pain threshold (TPT), pain tolerance threshold (TOL), response criterion, discriminative capacity)

Table 3 represents the mean values of all experimental pain ratings. An independent samples t-test was conducted to compare TPT and TOL between all FMS patients (n=24) and healthy controls (n=17). FMS patients showed a significantly lower TPT (m=41.1, SD=4.5) compared to healthy subjects (m=45.0, SD=4.4) $t(39)=2.8$, $p=0.01$. Also the TOL was significantly lower in FMS patients (m=44.7, SD=3.7) compared to healthy subjects (m=47.7, SD=3.7) $t(39)=2.5$, $p=0.02$. The one-way ANOVA considering 3 groups of subjects showed significant effects for TPT $F(2,38)=4.34$, $p=0.02$ and TOL $F(2,38)=3.7$, $p=0.03$. A post-hoc Gabriel test indicated that the FMS+ patients had significantly lower TPT ($p<0.02$) and TOL ($p<0.03$) than healthy subjects. The FMS- group did not significantly differ from the other two groups. The index of response bias (response criterion) and the discriminative capacity did not differ significantly between the three groups $F(2,35)=0.61$, $p>0.94$ (resp. $F(2,16)=1.18$, $p>0.33$ for discriminative capacity). Response criterion was not correlated with TPT (healthy subjects $p>0.6$, FMS- $p>0.07$ and FMS+ $p>0.9$) or TOL (healthy subjects $p>0.3$, FMS- $p>0.3$, FMS+ $p>0.09$). Discriminative capacity was not associated with TPT (healthy subjects $p>0.3$, FMS- $p>0.4$, FMS+ $p>0.2$) or TOL (healthy subjects $p>0.4$, FMS- $p>0.7$, FMS+ $p>0.2$) in any of the groups.

*Correlation of D2/D3 receptor availability with pain responses**Thermal Pain Threshold (TPT)*

In FMS+ patients, striatal D2/D3 receptor availability in the right nucleus caudate was negatively correlated with TPT ($r = -0.65$, $p < 0.03$) (see Figure 8). For the FMS- patients, however, no significant correlations with TPT could be determined ($p > 0.4$) (see Figure 9).

In healthy subjects, striatal D2/D3 receptor availability in the left putamen ($r = 0.53$, $p < 0.03$), left caudate nucleus ($r = 0.48$, $p < 0.04$), and left nucleus accumbens ($r = 0.5$, $p < 0.01$) was positively associated with TPT (see Figure 10).

Thermal Pain Tolerance (TOL)

No significant correlations between striatal D2/D3 receptor availability and TOL were found in any of the three groups ($p > 0.2$).

Response criterion

In healthy subjects and FMS+ patients no significant correlations of the response criterion with the D2/D3 receptor availability in any striatal region could be determined. In contrast, the FMS- patients showed a significant correlation of the subject's response criterion with the D2/D3 receptor availability in the right nucleus accumbens ($r = 0.72$, $p < 0.01$) (see Figure 11).

Discriminative capacity

The index of the subject's discriminative capacity, the area under the ROC curve, varied over a wide range between the subjects and did not differ between the three groups $F(1,38) = 2.1$, $p = 0.15$. Correlations of the discriminative capacity with the D2 receptor availability were not significant ($p > 0.17$) in any of the three groups.

Discussion

The major innovation of the present study was that it examined the link between striatal D2/D3 receptor availability and individual pain perception in patients with Fibromyalgia, both with and without comorbid MDD, compared to healthy subjects using the [^{11}C] raclopride PET method. To our knowledge, this is the first study investigating the link between striatal D2/D3 receptor availability and individual pain responses in Fibromyalgia that differentiated between individuals with and without depression.

Our main findings were (1) no differences in striatal D2/D3 receptor availability between FMS patients with depression and without depression compared to healthy subjects, (2) a positive association of the response criterion with D2/D3 receptor availability in the right nucleus accumbens in FMS without depression, (3) a negative correlation between striatal D2/D3 receptor availability in the right caudate nucleus and thermal pain threshold in FMS patients with depression, (4) a positive association of D2/D3 receptor availability in the left putamen, left caudate and left nucleus accumbens with thermal pain threshold in healthy controls, and (5) no correlations between D2/D3 receptor availability and discriminative capacity in any of the groups, and regions. Unexpectedly, we did not find any differences in D2/D3 receptor availability at rest across groups. This was also confirmed by a voxel-based (statistical parametric mapping, results not shown) analysis which was performed post-hoc to the ROI analysis and did not find any clear statistical effects. Our findings are at odds with previous studies which have demonstrated reduced presynaptic DA activity in FMS (Wood, Patterson, et al., 2007). There are several possible explanations for this. It is possible that these previous findings were influenced by methodological differences, i.e. pre-synaptic versus post-synaptic measures could explain these contradictory results. Furthermore, the reductions in 6-18F fluoro-L-DOPA uptake were limited to mesencephalon including ventral tegmental area and substantia nigra, suggesting that presynaptic neuronal integrity in the

mesencephalon is a more sensitive indicator of fibromyalgia than postsynaptic receptor sites. Moreover, these previous studies included smaller samples of patients and did not control for depression or other comorbid disorders. Additionally, lower raclopride BP in FMS patients than healthy controls in all functional sub-regions of the striatum during non-painful saline infusion have been reported (Wood, Schweinhardt, et al., 2007). However it is not entirely clear if this result reflects decreased DA receptor density or a greater release of DA in response to non-painful saline infusion and is therefore not directly comparable to our experimental paradigm. No study so far has investigated the baseline DA changes at the post-synaptic level in Fibromyalgia (i.e. in the absence of noxious stimuli). A recent study suggested the role of DA in modulating the salience of a pain stimulus rather than providing evidence for direct anti-nociceptive effects (Becker et al., 2013). Although dopaminergic mechanisms may differ in acute versus chronic pain, this proposed role of DA in mediating the motivational value of a pain stimulus may account for the associations unexpectedly found in our FMS groups and the absence of a difference in D2/D3 receptor availability at post-synaptic level. However, this is very speculative and should be investigated in future studies.

The Sensory Detection Theory analysis showed that Fibromyalgia patients with and without depression did not set a higher criterion for reporting pain and did also not differ in terms of discriminative capacity from our healthy controls. In addition, the thermal pain tolerance and thresholds of Fibromyalgia patients with depression differed from healthy controls but did not correlate with the response criterion or discriminative capacity. The results from the correlation analysis between D2/D3 receptor availability and psychophysical results in Fibromyalgia patients with and without depression are unexpected. Our results suggest a potential link between D2/D3 receptor availability and pain perception due to psychological factors in FMS which differ however between patients with and without comorbid depression. In Fibromyalgia patients without depression, D2/D3 receptor

availability in the right nucleus accumbens was positively associated with the criterion to report pain, but not with the index for discriminative capacity, thermal pain threshold or tolerance. Since the response criterion is a measure for psychological aspects of pain, the pain sensitivity in Fibromyalgia patients without depression appears to be determined mainly by a dopaminergic influence on psychological factors that in turn influence the subject's tendency to report pain rather than by physiological factors. In line with this finding psychological factors have been shown to have an important role in variability of pain ratings between subjects (Clark, 1974; Clark & Mehl, 1971). On the other hand cognitive and affective variables frequently occurring in FMS such as depression, anxiety or pain-related anxiety (Lachaine, Beauchemin, & Landry, 2010; Rutledge, Mouttapa, & Wood, 2009) were related to increased pain report and responses (Gil, Phillips, Edens, Martin, & Abrams, 1994). Also personality traits associated with FMS (Malin & Littlejohn, 2012) such as detachment, anxiety, and novelty seeking, were related to D2/D3 receptor availability (Breier et al., 1998; Farde, Gustavsson, & Jonsson, 1997; Suhara et al., 2001) and increased pain report (Farde et al., 1997). This matches the assumption that emotional and psychological processes may play a particularly important role in promoting pain in these patients (Geisser et al., 2003; Staud, 2004) and that affect may contribute to pain in FMS (Staud, Price, Robinson, & Vierck, 2004; Staud et al., 2003). In addition, D2 receptor-mediated neurotransmission in the ventral system involving the nucleus accumbens, has been shown to be associated with emotional processing of pain (Scott et al., 2006). Consistent with the possibility that psychological factors contribute to pain in FMS via DA transmission, it has recently been proposed that DA could play a role in modulating the salience of a pain stimulus (Becker et al., 2013), fostering coping responses, rather than having direct anti-nociceptive effects. This mediating role of DA might eventually explain why we found associations between striatal D2/D3 receptor availability in regions associated with emotional modulation of pain and psychophysical measures of emotional/attitudinal aspects of pain in our FMS patients. In Fibromyalgia

patients with depression, D2/D3 receptor availability in the right caudate was negatively associated with thermal pain threshold, but not with the response criterion or discriminative capacity. Evidence showing that D2 receptor-mediated neurotransmission in the dorsal caudate and putamen is associated with subjective ratings of sensory and affective qualities of pain (Scott et al., 2006), suggests that D2/D3 receptor availability in the right caudate of Fibromyalgia patients with depression influences non-sensory mechanisms underlying the pain response rather than actual pain sensitivity. These results are in line with a previous fMRI study which suggested that the presence of depression had no effect on the sensory-discriminative processing of pain stimulation but had a selective effect on brain regions that process the affective-motivational dimension of pain (Giesecke et al., 2005). Furthermore, this result and the fact that FMS patients with depression conveyed a lower pain threshold than the other subject groups, support the idea of a more pronounced deficit in pain inhibition in FMS with comorbid depressive symptoms (de Souza, Potvin, Goffaux, Charest, & Marchand, 2009), suggesting that depression could influence pain perception in FMS via DA. Our findings in Fibromyalgia patients with and without depression are not consistent with previous reports in healthy subjects where the pain threshold and the response criterion were inversely correlated with the D2/D3 BP in the human striatum (right putamen) (Pertovaara et al., 2004). The same study showed that the discriminative capacity is not a critical factor responsible for the association of pain responses with D2/D3 BP in healthy subjects (Pertovaara et al., 2004). This result is in line with our findings both in healthy subjects and Fibromyalgia patients. In accordance with our hypothesis, we found significant positive correlations between the thermal pain threshold and D2/D3 receptor availability in striatal regions including the left putamen, left caudate nucleus and the left nucleus accumbens in healthy subjects. This result however, contradicts previous findings that reported direct correlations between striatal D2/D3 receptors and pain thresholds in the right putamen (Martikainen et al., 2005) (Hagelberg et al., 2002; Pertovaara et al., 2004; Scott et al., 2006).

Lateralization differences in the DA system are well documented and an influence of gender on lateralization of the function of the DA system has previously been shown (Martin-Soelch et al., 2011). The deviation from the previous finding could therefore be explained by the inclusion of women in our study while the other studies included only men (Pertovaara et al., 2004). Furthermore, some pain-related phenomena such as pain threshold have been shown to occur with a laterality bias (Bar et al., 2005; Bar, Greiner, Letsch, Kobele, & Sauer, 2003; Leite-Almeida et al., 2012; Lugo, Isturiz, Lara, Garcia, & Eblen-Zaijur, 2002; Meh & Denislic, 1994). Moreover, associations between the D2 binding capacity and conditioned pain modulation, which reflects the capacity of the brain to inhibit and to modulate incoming pain signals, have been reported in the left putamen (Hagelberg et al., 2002).

Several previous PET studies also using [^{11}C] raclopride showed increased D2 receptor availability in chronic neuropathic pain conditions such as burning mouth syndrome (Jaaskelainen et al., 2001) or atypical facial pain (Hagelberg, Forssell, Aalto, et al., 2003). An overlapping pathophysiology between FMS and neuropathic pain has been suggested due to shared clinical features such as paresthesias, hyperalgesia and allodynia (Maletic & Raison, 2009; Martinez-Lavin, Lopez, Medina, & Nava, 2003), but our results indicate that striatal D2/D3 receptor availability in FMS patients with and without depressive symptoms are not impaired in the same way as in chronic neuropathic pain conditions.

Abnormal sensorial thresholds were also evidenced in neuropathic pain such as burning mouth syndrome or trigeminal non-idiopathic neuropathic pain (de Siqueira, Teixeira, & de Siqueira, 2013). Abnormal sensory findings are considered important features in the classification of neuropathic pain according to the International Association for the study of pain (IASP) (T. S. Jensen et al., 2011). Therefore, the observation of abnormal sensorial thresholds and the disrupted modulatory role of striatal D2/D3 receptors in pain processing in FMS could be added to other neuronal changes observed in these patients (for instance

impaired small fiber function in FMS) (Uceyler et al., 2013), contradicting the opinion that FMS is a pure somatization disorder without demonstrable abnormality.

Some limitations merit attention. This study did not allow for differentiation between D2/D3 receptor density or intrasynaptic dopamine concentration and the interpretation of underlying neuronal factors should be treated with caution. Prior work indicates that [^{11}C] raclopride values from the bolus method are almost identical to binding values generated by a bolus-infusion method (Carson, 2000; Watabe et al., 2000), in which DA release can be indirectly measured for the same subjects. Although SPM analysis of PET ligand studies is a viable alternative to ROI analysis, especially for the exploration of changes without a priori region definitions, requirements of the analysis include transformation of the PET data to standard anatomical space, smoothing of the data and quantitative normalization to account for global effects. In a small cohort as in our study, these processes may reduce the sensitivity to subtle changes in raclopride binding. Standardization of the basal ganglia anatomy for SPM analysis is a known challenge (in comparison to cortical anatomy). Therefore, our individual anatomy MR-based VOI analysis may be considered to better account for individual basal ganglia anatomy and improve the sensitivity of our PET measurements. Another limitation is that we did not include chronic neuropathic pain patients to control for similarities or differences between FMS and neuropathic pain. Further, we did not control for phases of menstrual cycle in our participants. However, the majority of the participants were postmenopausal (N=19, see Table 1). Finally, DA receptor binding results as well as the individual responses to pain may have been biased by the patients' medication, which possibly influenced the testing procedures, including slower reaction times and anti-nociceptive effects of antidepressants (N=12). Nevertheless, we found significant differences between FMS patients and healthy subjects with regard to the estimation of pain thresholds, and a previous study (Klauenberg et al., 2008) found no significant group difference

concerning SSRI medication regarding all pain thresholds. It is however possible that the lack of differences in D2/D3 receptor availability may be related to the medication.

Conclusion

To our knowledge, this is the first report on the association between D2/D3 receptor availability and pain perception in FMS, distinguishing between FMS patients with and without comorbid depression. Additionally, in comparison to previous studies in this field, our study included a relatively large sample of patients. In conclusion, our data suggest that there are no differences in D2/D3 receptor availability at rest between FMS patients with depression and without depression compared to healthy subjects. This study presents novel results suggesting that the association between D2/D3 receptor availability and pain perception differs between healthy subjects and patients with Fibromyalgia. Furthermore, this association also differed between FMS patients with and without depression, suggesting that depression could influence pain perception in FMS. Our results suggest that alterations in the dopaminergic system appear to be linked to pain sensitivity in FMS patients. Striatal D2/D3 receptor availability in Fibromyalgia patients with and without depression is associated with psychological aspects of pain rather than the discriminative capacity of the sensory system mediating pain. However, the exact mechanisms have yet to be elucidated and similarities with chronic neuropathic pain patients with regard to the modulatory function of DA in pain should be further explored. These findings contribute to the understanding of the function of the dopaminergic system in central pain processing in healthy individuals and in patients with FMS.

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Declaration of conflicts of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Appendix

Table 2. Demographic and clinical characteristics of subjects with Fibromyalgia (FMS without MDD N=13), (FMS with MDD N=11) and healthy controls (N=17)

Variable	FMS without MDD		FMS with MDD		Healthy controls		F	p
	Mean	SD	Mean	SD	Mean	SD		
Age	55.2	10.6	44.5	10.1	42.8	13.8	2.4	0.06
Education(years)	12.9	0.8	13.3	0.9	13.7	0.8	0.2	0.79
Duration FMS (years)	13.9	11.9	12.9	10.9				0.9
Tenderpoints	17	3.5	14.5	3.5				0.2
Duration MDD (years)	11.3	11.5						
BDI	7.9	3.9	17.3	8.6	1.4	1.8	28.9	0.001* ¹
SHAPS	0.7	0.5	2.1	0.5	0	0.4	0.8	0.015* ²
MADRS	5.9	1.5	15.5	9.4	0.3	0.7	30.5	0.001* ¹
PDI	18.7	10.6	25	6.7	3.1	7.7	18.1	0.001* ¹
Menopause		11		7		10		
Medication Antidepressants		4		9		0		

Notes. BDI = Beck Depression Inventory; SHAPS = Snaith Hamilton Pleasure Scale; MADRS =Montgomery Asberg Depression Scale; PDI= Pain disability index

ANOVA, level of significance two-tailed p<0.05

¹ healthy<FMS without MDD<FMS with MDD

² healthy<FMS with MDD

Table 3. Mean regional [^{11}C] raclopride striatal region/cerebellum ratios (SCR) for subjects with Fibromyalgia (FMS without MDD N=13), (FMS with MDD N=11) and healthy controls (N=17)

Region	FMS without MDD		FMS with MDD		healthy controls		F	p
	Mean	SD	Mean	SD	Mean	SD		
Putamen¹	5.2	0.5	5.2	0.6	5.2	0.7	0.005	0.9
Putamen²	4.9	0.8	5.1	0.4	5.1	0.8	0.49	0.6
ventral Striatum¹	4.1	0.8	3.7	0.8	3.5	0.9	2.01	0.1
ventral Striatum²	4.1	0.8	3.8	0.8	3.6	0.9	1.07	0.4
Caudate nucleus¹	3.2	0.8	3.6	0.8	3.7	0.7	1.72	0.2
Caudate nucleus²	3.9	0.4	4.1	0.5	3.9	0.7	0.32	0.7
nucleus accumbens¹	2.9	0.6	3.2	0.4	3.3	0.8	1.0	0.4
nucleus accumbens²	3.6	0.9	3.2	0.4	3.7	0.7	1.65	0.2

Notes. *ANOVA, level of significance two-tailed $p < 0.05$

¹ left

² right

Table 4. Means of thermal pain threshold, thermal pain tolerance and thermal Sensory Decision Indices (response criterion, discriminative capacity) for subjects with Fibromyalgia (FMS without MDD N=13), (FMS with MDD N=11) and healthy controls (N=17)

Variable	FMS without MDD		FMS with MDD		healthy controls		F	P
	Mean	SD	Mean	SD	Mean	SD		
Thermal pain threshold	41.9	5.1	40.1	3.65	45.01	4.4	1.5	0.02* ¹ (TPT) [C°]
Thermal pain tolerance	45.5	3.4	43.9	4	47.7	3.7	1.65	0.03* ¹ (TOL) [C°]
Response criterion	1.04	1.1	0.98	1.12	1.13	1.1	0.06	0.9
Discriminative capacity	0.51	0.13	0.59	0.12	0.57	0.15	1.05	0.35

Notes. *ANOVA, level of significance two-tailed $p < 0.05$

¹post-hoc test Gabriel: FMS with MDD < healthy controls

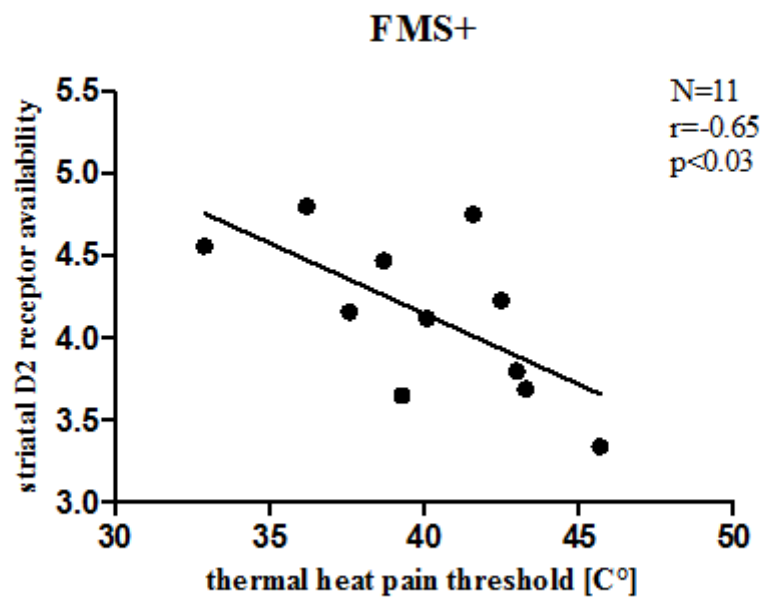


Figure 8. Association of striatal D2 receptor availability in the right nucleus caudate with thermal pain threshold in FMS patients with co-morbid MDD

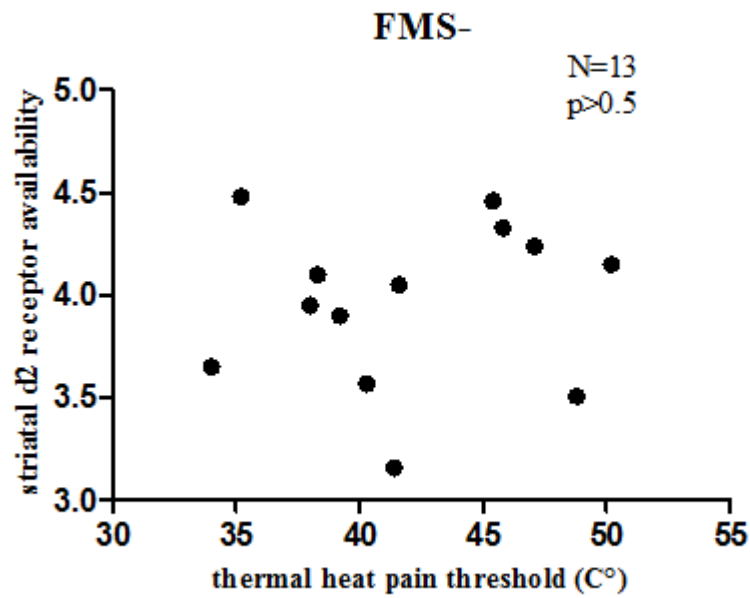


Figure 9. Lacking association of striatal D2 receptor availability and pain threshold in any striatal region of interest in FMS patients without co-morbid MDD (here displayed: striatal D2 receptor availability in right nucleus caudate)

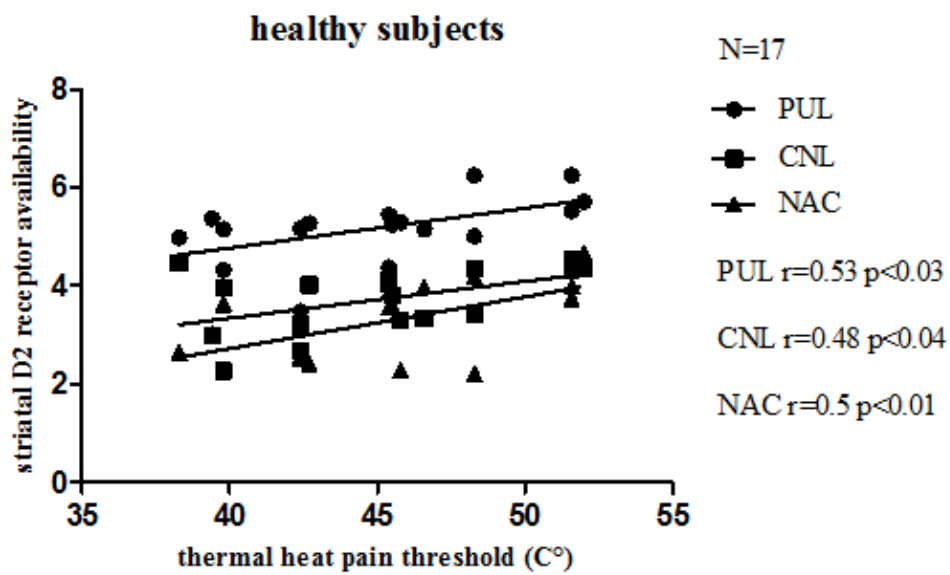


Figure 10. Association of striatal D2 receptor availability in the left putamen PUL, left caudate nucleus CNL, left nucleus accumbens NAC with thermal pain threshold in healthy controls

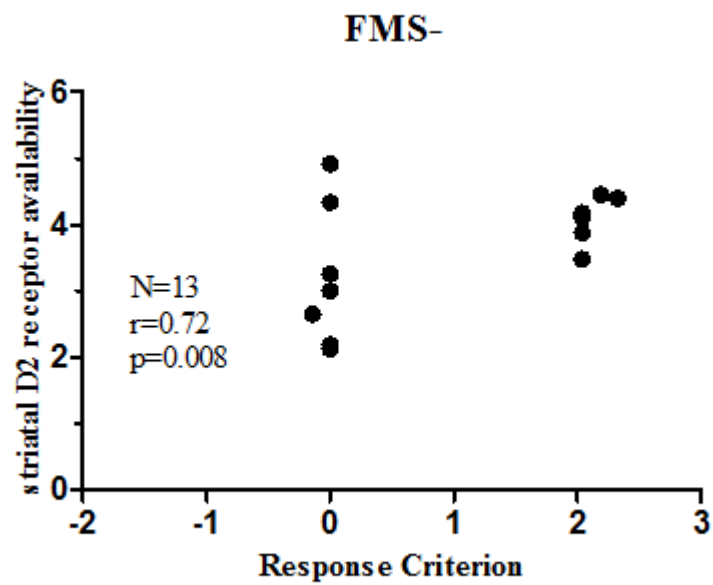


Figure 11. Association of striatal D2 receptor availability in the right nucleus accumbens with response criterion in FMS patients without co-morbid MDD

4. Increased Dopamine Release to Unpredictable Rewards in Female Fibromyalgia Patients with Comorbid Depression - a [¹¹C] Raclopride Bolus plus Infusion PET Study

Ledermann K.^{1,2}, Jenewein J.¹, Sprott H.³, Hasler G.⁴, Schnyder U.¹, Warnock G.⁵, Johayem A.⁵, Kollias S.⁶, Buck A.⁵, Martin-Soelch C.^{1,2}

¹ University Hospital Zurich, Department of Psychiatry and Psychotherapy, Zurich, Switzerland

² University Fribourg, Department of Psychology, Division of Clinical and Health Psychology, Fribourg

³ Painclinic, Basel, Switzerland

⁴ University Bern, Psychiatric University Hospital, Bern, Switzerland

⁵ University Hospital Zurich, Department of Nuclear Medicine, Zurich, Switzerland

⁶ University Hospital Zurich, Department of Neuroradiology, Zurich, Switzerland

Corresponding author:

Katharina Ledermann
University Hospital Zurich
Department of Psychiatry and Psychotherapy
Haldenbachstrasse 16/18
8091 Zurich (Switzerland)
Katharina.ledermann@usz.ch

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Abstract

Mesolimbic dopamine (DA) has been shown to be involved in the processing of pain and reward. Fibromyalgia syndrome (FMS), characterized by chronic widespread pain, is frequently associated with depression. Reduced DA function and reduced responses to reward were also evidenced in depression. First evidence suggests that chronic pain might impair reward processing. Therefore, reduced DA reaction to reward could be involved in depressive symptoms and pain symptoms observed in FMS. We tested here whether striatal DA responses to monetary rewards would be impaired in FMS patients compared to healthy controls and whether this reduction would be stronger in FMS patients with co-morbid depression (MDD). In 24 female FMS patients (11 with MDD) and 17 healthy controls, differences in regional D2/3 receptor binding potential (ΔBP) between an unpredictable reward condition and a sensorimotor control condition were measured using the bolus-plus-constant-infusion [^{11}C] raclopride method. The ΔBP was assessed in MRI-based striatal regions-of-interest and compared between FMS patients with and without MDD and healthy controls.

We found significant reductions in binding potential (BP_{ND}), presumably reflecting increased dopamine release, in the reward vs. the control condition in the right nucleus accumbens and right caudate nucleus. This reduction in the right nucleus accumbens was more prominent in FMS patients with co-morbid MDD compared to healthy controls. Among FMS patients, this reduction in the right caudate nucleus was significantly more prominent in those with co-morbid MDD relative to those without MDD. The collapsed FMS group had a significantly greater ΔBP than healthy controls in the right nucleus accumbens. This study showed that FMS patients had an increased reaction to rewards that was more accentuated in patients with MDD, suggesting that FMS patients exhibit dysfunctional DA responses to monetary rewards relative to healthy controls.

Introduction

Numerous neuroimaging studies show that pain and reward are mediated by similar neural pathways in the central nervous system (for review see (Becker et al., 2012)) involving a complex network of subcortical and prefrontal structures which are both related to the dopamine (DA) and opioid systems (Borsook et al., 2007; Kut et al., 2011; Leknes & Tracey, 2008). It is well documented that the mesolimbic DA system is involved in reward processing (Haber & Knutson, 2010; Hudson, Arnold, Keck, Auchenbach, & Pope, 2004). Several studies demonstrated that rewards, including pleasurable stimuli or activities and positive affective states, have an analgesic effect (Lewkowski et al., 2008; Roy et al., 2009; Villemure & Bushnell, 2009). Chronic pain seems to alter brain systems that process pain and reward, possibly affecting the pain-reward interactions (Becker et al., 2012). These findings maintain a mutual influence of rewarding and painful stimuli that could be mediated through the DA system. There is a high rate of co-morbidity between chronic pain and depression (Fishbain, Cutler, Rosomoff, & Rosomoff, 1997; Wilson, Eriksson, D'Eon, Mikail, & Emery, 2002); the prevalence of depression in chronic pain exceeds 20% (Fishbain et al., 1997; Wilson et al., 2002) and often includes anhedonia, i.e., the reduced ability to enjoy pleasurable activities (Marbach & Lund, 1981), which has been shown to be related to a dysfunction of the mesolimbic DA system (Sarchiapone et al., 2006). Additionally there is a large body of evidence showing that the DA system is impaired in major depressive disorder (MDD) (Martin-Soelch, 2009). Disrupted physiological, behavioral and subjective aspects of reward function are postulated to be critical to the development and pathophysiology of depression (Forbes & Dahl, 2012; Hasler, Drevets, Manji, & Charney, 2004). However, the precise mechanisms of the mutual pain-reward interaction are still not fully understood and only a few studies investigated the influence of pain on reward respectively of rewards on pain in humans (Leknes & Tracey, 2008), (Becker et al., 2012).

A dysfunction of DA has been evidenced in chronic pain patients including higher DA D2 receptor availability in neuropathic pain and reduced presynaptic DA function in Fibromyalgia (FMS) (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg et al., 2004; Wood, Patterson, et al., 2007). FMS is an idiopathic, diffuse soft-tissue pain syndrome characterized by lowered pain thresholds in the area of tendons and other pain-related symptoms such as fatigue, sleep disruption, cognitive impairment and gastrointestinal symptoms (Wolfe, 1990). Major depressive disorder (MDD) is the most frequent co-morbidity in FMS (Fietta et al., 2007). Despite its high clinical significance, the neural correlates and the interaction between psychological and neurobiological processes in the pathophysiology of FMS are still poorly understood. Finally the influence of chronic pain symptoms as experienced in FMS on the ability to enjoy reward has not been investigated yet.

We tested here the endogenous DA release associated with unpredictable monetary rewards during bolus-plus-infusion [^{11}C] raclopride PET scanning using a validated reward task (Caine & Koob, 1994) in FMS patients without co-morbid MDD (FMS-), with co-morbid MDD (FMS+) and healthy controls to investigate if FMS is associated with dysfunction of the central reward system. We postulated that the healthy controls would evidence an increase of striatal DA transmission in response to unpredictable reward and that this increase would be reduced in FMS patients. Furthermore, we expected FMS+ patients to show a stronger reduction of this effect than FMS- patients. Additionally, we hypothesized that depression, anhedonia and pain disability scores would correlate negatively with DA release in response to rewarding stimuli.

Material and Methods

Research subjects

A description of clinical and demographic data parameters for the FMS patients is summarized in Table 1. A total of 24 FMS patients fulfilling the American College of Rheumatology (ACR) classification criteria for Fibromyalgia (Beck et al., 1961; Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, et al., 1990) and 17 age- and gender-matched medically and psychiatrically healthy controls were included in the study. Among the FMS patients 11 subjects met the DSM-V criteria (American Psychiatric Association, 2013(APA)) for MDD (current and lifetime depressive episode). All subjects were tested for comorbid psychiatric disorders using the SCID (Structured Clinical Interview for DSM-IV; (First, 2002)). This instrument was also used to diagnose MDD in the FMS group. All FMS+ patients had the onset of MDD subsequent to the FMS diagnosis. All FMS patients had their FMS diagnosis confirmed by an experienced rheumatologist (HS) through clinical examination, including measurements of pain thresholds at tender points using a digital dolorimeter (LD 100 NRS, AC Engineering Basel, Switzerland). A description of clinical and demographic data parameters for the FMS patients is provided in Table 1. Exclusion criteria were current and/or chronic medical conditions, current and/or lifetime psychiatric diagnoses, general MRI and PET exclusion criteria, pregnancy (pregnancy test on the day of scanning), breast-feeding and medication other than oral contraceptives for FMS patients and the controls. In addition, controls were excluded if they had diagnoses of acute or chronic pain. FMS subjects were allowed to continue their SSRI (selective serotonin reuptake inhibitors), TCA (tricyclic antidepressants) and NSAID (non-steroidal anti-inflammatory drugs) medication during the study. A total number of 12 FMS patients were taking antidepressant medication either for pain or depressive symptoms. The use of opioids, neuroleptics, antiepileptics and lithium was an exclusion criterion.

All participants were required to sign an informed consent which explained the procedures of the study prior to information and testing. The study was approved by the Ethical Committee of the Canton Zurich and the Swiss Federal Department of Health (Bagatzounis et al.) in accordance with the current version of the declaration of Helsinki (Rickham, 1964) and the Swiss regulatory's requirements.

Experimental conditions

To measure the endogenous DA release to unpredictable rewards we used a slot-machine task adapted from Martin-Soelch et al. (Martin-Soelch et al., 2011) (see Figure 1) that involved two conditions, a sensorimotor task followed by a reward condition, each consisting of 180 trials, each of an average duration of 8s. In the monetary-reward condition subjects received financial reward unpredictably, in a pseudo-randomized order with an average of one reward per four trials. In the sensorimotor control condition subjects performed the same task without receiving rewards. The sensorimotor condition served as control for motor activation and other nonspecific aspects of task performance. Before scanning, subjects performed a short practice session of each task. During scanning subjects rested for the initial 20 min to allow [^{11}C] raclopride to approach equilibrium. The ability of this design to induce equilibrium and task-related changes in raclopride binding was tested by Martin-Soelch et al. (Martin-Soelch et al., 2011) and confirmed by Savitz et al. (Savitz et al., 2013) During the subsequent 24 \pm 2min subjects performed the sensorimotor control task. Beginning 50min after the start of the [^{11}C] raclopride infusion, subjects performed the monetary reward condition for 24.1 \pm 1.7min. This timing allowed the distribution of [^{11}C] raclopride to reach equilibrium for each of the two task conditions during the scanning epochs described below. During the 24min epochs that corresponded to each task condition, subjects

alternated between 2-min periods in which they actively performed the task and 1-min periods when they rested to minimize fatigue. Each subject won a total of 54 SFr. (62 USD) during the rewarded condition, which they received in cash following the study.

Behavioral assessments

During the slot machine task (once in each condition only) participants rated their currently perceived pain intensity using a horizontally oriented visual analog scale (VAS), ranging from 0 (no pain at all) to 5 (most intense pain imaginable). Before beginning image acquisition, participants were familiarized with the rating scales to ensure that they used the scales appropriately. All pain ratings during the behavioural task are shown in Table 4.

PET image acquisition

The D2/D3 receptor antagonist [^{11}C] raclopride was produced on site according to Good Manufacturing Practice (GMP) guidelines. The PET examinations were performed on a full ring PET/CT scanner with an axial field of view of 15.3 cm in 3D mode (Discovery DSTX, GE Healthcare, Waukesha, WI, USA) at the Department of Nuclear Medicine at the University Hospital Zurich, Switzerland. The emission data was corrected for attenuation, scatter, randoms, and dead time using the corresponding CT (120 kV/80 mA), and reconstructed using a standard iterative algorithm (ordered set expectation maximization [OSEM]). The [^{11}C] raclopride (415 \pm 30 MBq) was administered as an initial bolus over 60s after Watabe et al. (Watabe et al., 2000), followed by a maintenance infusion over the remainder of the scanning session (a total of 90 min) using a computer-operated pump (Arcomed, syramed μ SP600, Regensdorf, Switzerland). Dynamic emission scanning (41 frames of 0 to 6000 seconds (i.e. 100 min scan), framed as 4 x 15, 8 x 30, 9 x 60, 2 x 180, 4 x

300, 6 x 200, 8 x 300 sec) was initiated with injection of the [^{11}C] raclopride bolus. BP_{ND} in a resting state was measured in all participants one week before the B/I [^{11}C] raclopride PET scan and the results are described in Ledermann et al. under review.

Magnetic resonance imaging

Each subject received a high-resolution T1 weighted magnetic resonance scan (3D fast-field echo scans with 160 slices, 1mm isotropic resolution, TR= 18ms, TE= 10ms, flip angle = 30°) on a 3 tesla Philips Achieva scanner (Philips Medical Systems) for co-registration with PET images. All images were checked for structural abnormalities and lesions by a clinical neuroradiologist.

PET imaging data analysis

ROI analysis

PMOD software Version 3.2 (PMOD Technologies Ltd, Zurich, Switzerland) was used for PET data analysis. As an initial step, we corrected for possible head motion-induced artifacts during the 100 min. PET acquisition were performed with a mutual information registration of each image frame to a standard frame (10-15 min after injection) before attenuation correction. Based on the calculated motion, the transmission images were resliced and projected for final attenuation correction, reconstruction and realignment. The realigned frames acquired during the first 8 min of scanning, during which the radiotracer distribution was most sensitive to cerebral blood flow (CBF) so that cortical outlines were sufficiently evident to guide image co-registration, were summed to generate an image that was co-registered to the corresponding MRI image using PMOD software. The delivered

transformation matrix was applied to the composite images consisting of (i) baseline (frames acquired between 40 and 50 min) and (ii) the reward condition images (frames acquired between 60 and 80 min), which were acquired under equilibrium conditions achieved as subjects performed the sensorimotor control and monetary reward tasks (Fig. 1), respectively, after Martin-Soelch *et al.* (Martin-Soelch *et al.*, 2011). Using a region-of-interest (Abulencia *et al.*) approach, mean tissue radioactivity concentrations from baseline and reward images were extracted using MRI-based regions of interest (ROIs), defined on a template MRI image using PMOD software (PMOD Technologies Ltd, Zurich, Switzerland) in the anteroventral striatum, ventral putamen, dorsal putamen, middle caudate, dorsal caudate, nucleus accumbens and cerebellum (Fig. 2), after Drevets *et al.* (Drevets *et al.*, 2001; Drevets *et al.*, 1999). Each individual MRI was registered to the template brain and the ROI's were repositioned as needed to accommodate for individual differences in anatomy. The anatomical accuracy and symmetry of each set of individual ROI's was verified by a neuroscientist familiar with striatal anatomy (C.M.S). These ROI's were then back-transformed into the subject's native MRI space and applied to the co-registered PET images. Mean radioactivity in the reference region (cerebellum; C') was used to control for the effects of free and non-specifically bound [^{11}C] raclopride. The [^{11}C] raclopride binding potential (BP_{ND}), which is inversely correlated to endogenous DA release, was chosen as the measurement of D2 receptor binding for each brain region.

Decay-corrected tissue radioactivity concentrations were obtained from each ROI using a calibrated phantom standard to convert tomographic counts to becquerels per millilitre. C', the mean radioactivity in the reference region (cerebellum) was used to factor out the effects of free and non-specifically bound [^{11}C] raclopride. The percentage change in [^{11}C] raclopride binding was computed as the difference in $\text{BP}_{\text{ND(non-displaceable)}}$ between baseline and reward images after Watabe *et al.* (Watabe *et al.*, 2000) using the following equation for ΔBP .

$$\Delta BP = \frac{\frac{(C_{\text{reward}} - C'_{\text{reward}})}{C'_{\text{reward}}} - \frac{(C_{\text{baseline}} - C'_{\text{baseline}})}{C'_{\text{baseline}}}}{\frac{(C_{\text{baseline}} - C'_{\text{baseline}})}{C'_{\text{baseline}}}} \times 100$$

The obtained negative values of [¹¹C] raclopride ΔBP indicated the percentage of displacement of [¹¹C] raclopride by endogenously released DA, with the greater negative values corresponding to greater [¹¹C] displacement.

To test the significance of ΔBP in each region and each group, we used one sample t-tests.

The *a priori* hypothesis was tested using one-factorial ANOVA with group as factor on the ΔBP obtained in striatal regions of interest, with a null hypothesis that there is no effect of group. Between-group comparisons of ΔBP for the collapsed FMS group were conducted using one-way ANOVA. A repeated measure ANOVA with factors region and laterality and group as between subject factor was performed to assess differential responses between regions. Additional analyses explored correlations between depression (BDI, MADRS), anhedonia (SHAPS), anxiety (STAI) and pain disability (PDI) scores and ΔBP. To assess the difference in pain ratings between sensorimotor control and reward condition repeated ANOVA's with between-subject-factor group were performed.

Results

The participants' demographic and clinical data are summarized in Table 1. There were no significant differences in mean age and education between the FMS patient groups and the healthy controls. Tender point evaluation and duration of illness were similar across FMS groups. Measures for pain, depression, anhedonia and anxiety were typically elevated in

the FMS patients groups, but depression and pain ratings were significantly greater in FMS+ compared to FMS- and healthy controls. Anhedonia scores were significantly elevated in FMS+ compared to healthy controls. Pain ratings showed no main effect of condition ($p=0.6$) and no interaction of group x condition effect ($p=0.9$). The between-subject-factor group reached significance $F(2,37)=16.6$, $p<0.001$. Gabriel post hoc tests indicated significant greater pain ratings in FMS + patients compared to healthy subjects and FMS- patients and between healthy subjects and FMS- patients.

ROI analysis

Mean regional binding potential (BP_{ND}) values for each condition and mean changes in BP_{ND} between conditions and ΔBP are presented in Table 5. Plot of mean percentage change in binding potential (ΔBP) in the ROI analyses are shown in Figure 13.

Significance of ΔBP in each region and each group

One-sample t-tests yielded statistically significant differences (Bonferroni corrected) between mean percentage changes in binding potential and the assumed null value in all regions of interest. Left putamen $t = 11.878$, $SEM = 16.335$, $p < 0.001$ (two-tailed); right putamen $t = 8.007$, $SEM = 15.23918$, $p < 0.001$ (two-tailed); left ventral striatum $t = 2.963$, $SEM = 10.97483$, $p = 0.005$ (two-tailed); right ventral striatum $t = 7.985$, $SEM = 16.65482$, $p < 0.001$ (two-tailed); left caudate nucleus $t = 3.316$, $SEM = 13.67215$, $p = 0.002$ (two-tailed); right caudate nucleus $t = 10.059$, $SEM = 16.92849$, $p < 0.001$; left nucleus accumbens $t = 2.616$, $SEM = 13.05666$, $p = 0.013$ (two-tailed), right nucleus accumbens $t = 12.055$, $SEM = 29.95337$, $p < 0.001$ (two-tailed). One-sample t-tests yielded statistically significant differences

(Bonferroni corrected) between mean percentage changes in binding potential and the assumed null value in all groups $t=6.400$, $SEM=0.820$, $p<0.001$ (two-tailed).

Baseline group differences

No baseline group differences in striatal D2/3 receptor availability at rest between FMS+ and FMS- patients compared to healthy controls have been found as described in a companion paper (Ledermann et al. under review).

Group differences for ΔBP in the collapsed FMS group

Considering all FMS participants together in a group significant reductions in BP_{ND} in the reward vs. the control condition in the right nucleus accumbens $F(1,39)=5.98$ $p=0.019$ were found and the ΔBP was significantly greater in FMS patients compared to healthy controls (collapsed FMS group).

Group comparison for ΔBP (separating between FMS+ and FMS-)

We found significant effects on ΔBP in right caudate nucleus ($p=0.024$) in all participants. Post-hoc test Gabriel showed that mean ΔBP was significantly greater in FMS+ compared to FMS-, but not between controls and FMS+ resp. FMS-. The mean ΔBP in the right nucleus accumbens differed significantly between groups ($p=0.013$). Post-hoc test Gabriel showed that mean ΔBP was significantly greater in FMS+ compared to healthy controls but no significant group difference was found for the FMS- group.

Influence of region and laterality

The repeated measures ANOVA with factors region and laterality and between-subjects factor group showed significant main effects for region $F(1,37)=7.7$, $p<0.008$ and laterality $F(1,37)=6.07$, $p=0.018$. The interaction between region and laterality was significant $F(1,37)=9.3$, $p<0.004$. The between subject factor group did not reach significance $F(2,37)=1.1$, $p=0.333$.

Correlations between depression, anhedonia, anxiety and pain disability scores with ΔBP during sensorimotor control and reward condition

No significant correlations were found in regions showing significant changes in [^{11}C] raclopride binding. However, the only significant correlations were a significant correlation between ΔBP in the left nucleus accumbens and SHAPS ($r=0.56$, $p<0.045$) and a trend for a negative correlation between ΔBP in the left nucleus accumbens and PDI ($r=-0.54$, $p=0.057$) in the group of FMS- patients. No other significant correlations could be found.

Discussion

In this study, we investigated endogenous DA release during unpredictable monetary rewards in FMS patients with and without co-morbid depression and age- and gender-matched healthy subjects. Using the [^{11}C] raclopride Bolus- plus-infusion PET method and a validated slot-machine task, we surprisingly found a greater percentage of displacement of [^{11}C] raclopride in the right nucleus accumbens by endogenously released DA in all FMS patients that was more accentuated in patients with co-morbid depression. FMS patients with co-morbid MDD compared to healthy controls. Moreover, FMS patients with co-morbid depression showed greater reductions in [^{11}C] raclopride binding in the reward vs. the

sensorimotor conditions in the right nucleus caudate compared to FMS patients without depression. In sum these results suggest: 1) that FMS patients have a dysfunctional neurochemical response to reward information; 2) that unpredictable monetary rewards elicit an increased DA reaction in the controls and the FMS patients, which was more accentuated in the patients; and 3) that the dysfunctional reward circuitry could be associated with co-morbid depression in the pathology of FMS. Behaviourally, FMS patients had elevated depression and pain scores, and FMS patients with co-morbid depression showed evidence of anhedonia, the inability to experience pleasure. No significant correlations between regions showing differences in DA release and depression, anhedonia and pain scores could be determined. Pain ratings during the task were greater in all FMS patients, but there was no evidence of decreased pain intensity following unpredictable rewards as has been shown previously for appetitive stimuli (Rhudy, Williams, McCabe, Nguyen, & Rambo, 2005; Rhudy, Williams, McCabe, Rambo, & Russell, 2006). These observed reductions in binding potential could reflect differences between groups in the neural processing of obtaining rewards. [^{11}C] raclopride is sensitive to competition from endogenously released dopamine in response to tasks that induce dopamine release. In this study, the observed decreases in binding potential are, therefore, likely secondary to dopamine release in response to unpredictable monetary rewards obtained in the slot-machine task. However, DA has been shown not to be responsible for the processing of rewarding stimuli per se, but specifically for the motivation to obtain rewards (Barbano & Cador, 2007; Berridge, 2007). Previous studies reported decreased reward sensitivity and/or decreased motivation in rats with neuropathic (Ozaki et al., 2002) and arthritic pain (Ji et al., 2010; Pais-Vieira, Mendes-Pinto, Lima, & Galhardo, 2009). Furthermore, impaired decision making based on reward and punishment in patients with chronic back pain and complex regional pain syndrome (CPRS) (Apkarian et al., 2004), impaired operant learning of pain sensitization and habituation in FMS (Becker et al.,

2011) and reduced reward/punishment signaling in FMS in the ventral tegmental area (Loggia et al., 2014) have been reported. Although previous PET [^{11}C] raclopride studies of DA release during reward processing did not involve chronic pain patients or FMS patients, our findings are partly compatible with their results. Martin-Soelch et al. (2011), using the same method in a group of healthy subjects, found the strongest [^{11}C] raclopride decrease in response to unpredictable rewards in the right nucleus accumbens (Martin-Soelch et al., 2011). Furthermore, associations between DRD3Ser9Gly polymorphism and DA release in response to unpredictable rewards in the right nucleus accumbens in a sample of healthy controls and patients with MDD were reported (Savitz et al., 2013). This is the same region where we found significant differences between healthy controls and FMS patients with co-morbid depression and between healthy controls and the whole FMS group. The differences in the caudate nucleus are in line with a study of reward in MDD sharing differences in the neural responses to reward in the caudate nucleus and nucleus accumbens (Pizzagalli et al., 2009). However, this study and also other studies investigating MDD in reward tend to indicate a decreased neural response to reward. In contrast, our findings in FMS patients with co-morbid MDD are at odds with studies delineating striatal response to reward in individuals with MDD (Dichter, Kozink, McClernon, & Smoski, 2012; Forbes et al., 2009; Nestler & Carlezon, 2006; Pizzagalli et al., 2009; Stoy et al., 2012; Zhang, Chang, Guo, Zhang, & Wang, 2013). They typically found lower levels of striatal response in individuals with MDD compared to individuals without MDD. These findings indicate a loss of reward function that drives symptoms such as anhedonia. The presence of accentuated striatal DA response in our FMS patients with co-morbid MDD is therefore unexpected as depression, chronic pain and anhedonia have been found to be associated with low responsiveness to reward cues (Dawkins, Powell, West, Powell, & Pickering, 2006; Nutt et al., 2007). However, one possible explanation for these findings might be that the responsiveness of the phasic DA

system is regulated by tonic (extrasynaptic) DA levels. Tonic DA levels are modulated by presynaptic limbic and cortical glutamatergic inputs as well as DA neurons in the ventral tegmental area (VTA) (Grace, 1991; Howland, Taepavarapruk, & Phillips, 2002) and low tonic DA levels facilitate phasic DA firing (Grace, 1991). This fits well with reports of DA hypofunction in FMS in particular with reduced presynaptic DA activity in limbic cortex and VTA (Wood, Patterson, et al., 2007; Wood, Schweinhardt, et al., 2007). Furthermore, low levels of DA in the central DA system are experienced as aversive (De Witte, Pinto, Ansseau, & Verbanck, 2003) and increased DA activity is associated with pleasurable affective states (Ashby, Isen, & Turken, 1999). It is therefore conceivable that the attenuated DA reaction in our FMS patients is due to an up-regulation of the mesolimbic DA system stemming from an under activation of striatal and prefrontal DA projections in the mesolimbic DA system.

In addition, these results might also have important implications for understanding the specificities of FMS subgroups according to depressive symptoms and individuals with MDD. While FMS and MDD have been shown to share common features both at physiological and psychological levels (for review see (Gracely, Ceko, & Bushnell, 2012)), our results suggest that FMS and MDD are related to different pathophysiological mechanisms on a neurobiological level.

In sum, these findings add to the growing body of literature supporting the notion of the mesolimbic DA system dysfunction in the pathophysiology of FMS. Our results are in line with other studies showing altered dopaminergic neurotransmission in FMS patients. For instance, recent PET studies have demonstrated that FMS patients exhibit reduced activity levels of DOPA decarboxylase, an enzyme involved in dopamine metabolism, in several regions including the ventral tegmental area (Wood, Patterson, et al., 2007). Reduced dopaminergic brain responses to evoked pain have been reported in FMS patients compared to healthy controls (Wood, Schweinhardt, et al., 2007). A recent fMRI study reported reduced

reward/punishment signaling in FMS in the ventral tegmental area (Loggia et al., 2014). Our findings extend prior reports of alterations of pain reward interactions with chronic pain (Becker et al., 2012; Loggia et al., 2014) and suggest that there are differences between FMS patients with and without co-morbid MDD on a neurobiological level. In chronic pain the process of a reward deficit syndrome may relate to ongoing circuit dysfunction as increasing evidence suggests that plasticity of neural circuits are responsible for subtle changes over time, contributing to the behavioral manifestation of altered affective processes including blunting of reward or enhancing depression.

Strengths and limitations

To the best of our knowledge, this is the first study to investigate the dopaminergic response to unpredictable rewards in patients with FMS and no study so far addressed the question of the common neural basis of pain, reward processes and underlying depression in FMS. One strength of the current study is the relatively large number of FMS subjects who completed the study. This allowed comparing FMS patients with and without co-morbid depression systematically on the basis of standardized diagnostic methods. Furthermore, by using the [^{11}C] raclopride Bolus-plus-infusion PET method and a validated slot-machine task, we were able to measure endogenous DA release *in vivo* in response to unpredictable monetary rewards.

Several limitations of our study design merit comment. First, patients were allowed to continue their medication. Recent evidence suggests that SSRIs can reduce striatal activation under reward conditions, whereas drugs that impact on the norepinephrine system accentuate this response (McCabe, Mishor, Cowen, & Harmer, 2010). Second, the phase of menstrual cycle in which female subjects were examined was not fixed and we did not evaluate

differential effects of distinct menstrual phases on reward-induced DA release. However, 28 of the participants were post-menopausal.

Conclusions

The current study identified differences in endogenous DA release during unpredictable monetary rewards in FMS patients with and without co-morbid depression and age- and gender matched healthy subjects. In sum, FMS patients exhibited dysfunctional DA responses to unpredictable monetary rewards relative to healthy controls. However, the finding of an increased response to rewarding stimuli in FMS patients with co-morbid depression is new. Our findings extend previous research on impairments of chronic pain in several aspects of reward processing and show that FMS patients with co-morbid depression may be distinguished from those without depression on a neurobiological level. Further, we found that FMS patients with MDD exhibited different DA release patterns than patients with MDD. These findings have important implications for identifying both common and distinct properties of the neural circuitry underlying FMS with and without co-morbid MDD and provide important insights toward a better understanding of the etiology of this prevalent and debilitating disorder. Moreover, these findings suggest that interventions to restore DA regulation could be therapeutically beneficial in FMS patients.

Acknowledgements

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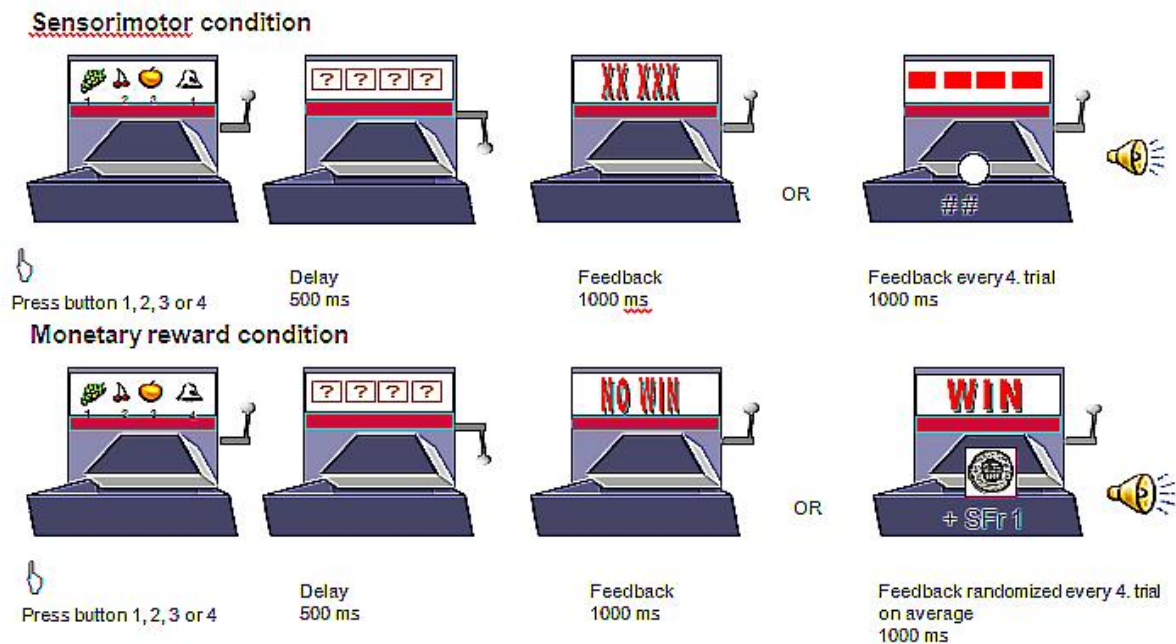


Figure 12. Illustration of the experimental task adapted from (Martin-Soelch et al. 2011)

During each trial, subjects were presented four distinct pictures (apple, grape, cherry, bell) presented in a “slot-machine” motif. Subjects were asked to choose one of the four with a button press on a four-button response box using the right hand. This response was followed by a 0.5 second delay. In the rewarded trials a 1 SFr. coin appeared for 1 second and subjects heard the characteristic sound of an opening cash-register door. These monetary gains were provided in a pseudo-randomized order with an average of one reward per every fourth trial. In the sensorimotor control trials, subjects instead were presented a meaningless symbol accompanied by a “click” sound on every fourth trial. After receiving the trial outcome subjects were presented their running total of earnings for 1 second. Displaying the actual balance account prevented rapid discounting of the rewards presented. At the end of each trial subjects viewed a blank screen for 1 second. During the reward task subjects were unaware of which trial or picture would lead to the receipt of a reward, except that the same picture could

not provide a reward in two consecutive trials. Subjects thus were instructed not to select the same picture more than twice in a row (selection of the same picture twice-in-a-row led to interruption of the task, and the task continued only after another picture was selected). In the sensorimotor control condition the subjects performed the task without receiving any reward, and in the monetary reward condition the subjects received monetary rewards in an unpredictable fashion.

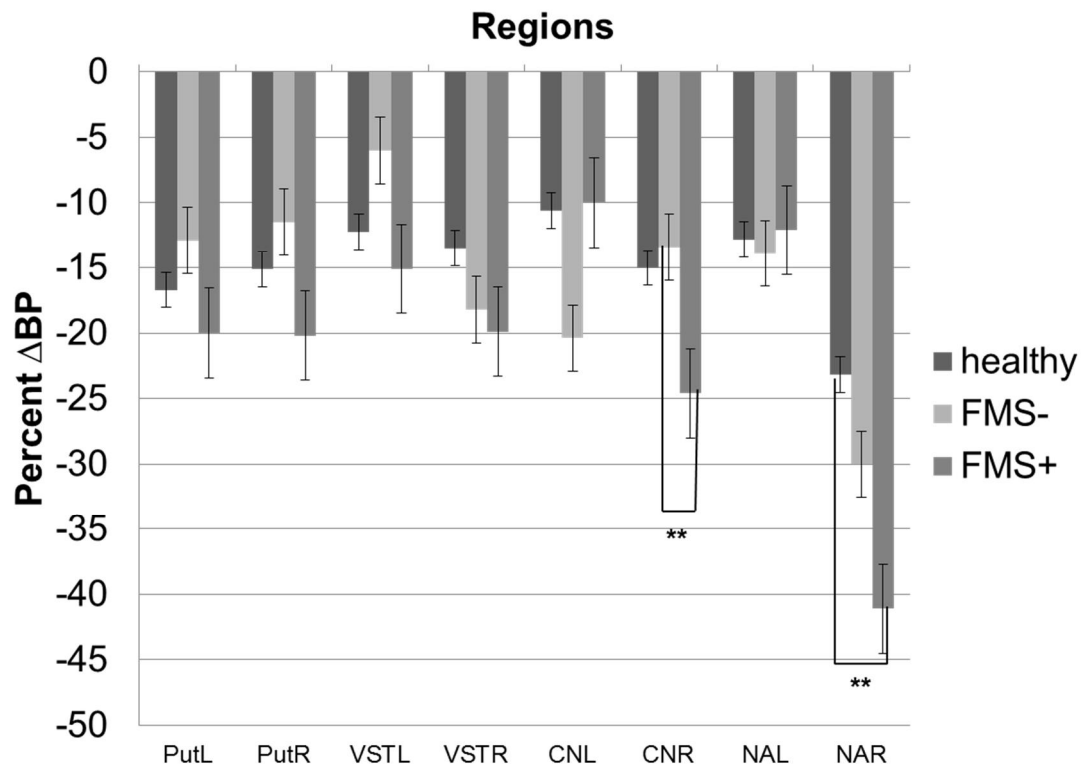


Figure 13. Reward-related changes in regional binding potentials for [^{11}C] raclopride. Plot of mean percentage change in binding potential (ΔBP) in the ROI analyses. A significant group difference was evident in the right caudate nucleus and the right nucleus accumbens. Post-hoc tests indicated a significant difference in ΔBP between FMS+ and FMS- patients in the right caudate nucleus and between healthy controls and FMS+ in the right nucleus accumbens. PutL, left putamen; PutR, right putamen; VSTL, left ventral Striatum; VSTR, right ventral striatum, CNL, left caudate nucleus; CNR right caudate nucleus, NAL, left nucleus accumbens; NAR right nucleus accumbens

Table 5

Mean pain ratings during PET measurement for each condition for subjects with Fibromyalgia (FMS without MDD N=13), (FMS with MDD N=11) and healthy controls (N=17)

	FMS without MDD		FMS with MDD		Healthy controls		p-value
	Sensorimotor condition Mean (SD)	Reward condition Mean (SD)	Sensorimotor condition Mean (SD)	Reward condition Mean (SD)	Sensorimotor condition Mean (SD)	Reward condition Mean (SD)	
Pain rating	2.91 (1.24)	2.83 (0.93)	3.18 (0.98)	3.09 (0.7)	1.29 (0.98)	1.29 (0.98)	0.01*

*level of significance two-tailed $p < 0.05$ for the between subject-factor group in the repeated measures ANOVA for pain ratings during the PET measurement

Table 6

Mean regional binding potential (BP_{ND}) values for each condition and mean changes in BP_{ND} between conditions for subjects with Fibromyalgia (FMS without MDD N=13), (FMS with MDD N=11) and healthy controls (N=17)

			(Δ			(Δ			(Δ	

*Levels of significance (two-tailed) are given for the ANOVA for the between group comparisons of ΔBP
¹ left ² right

5. General discussion

Converging evidence from preclinical, epidemiological, neuroimaging and genetic studies points to a role for DA neurotransmission in modulating pain perception and analgesia (Jarcho et al., 2012; Wood, 2008). Further, findings suggest that pain and reward are mediated by similar neural pathways in the CNS involving a complex network of subcortical and prefrontal structures related to both the DA and the opioid systems that influence each other on a neurobiological and motivational level (Borsook et al., 2007; Kut et al., 2011; Leknes & Tracey, 2008). An involvement of DA in the processing of rewarding information is well documented (Haber & Knutson, 2010). Recent findings suggest that pain, in particular long-term pain, might impair several aspects of reward processing (Becker et al., 2012; Loggia et al., 2014). It has been suggested that a dysregulation in DA signaling may modulate the experience of pain both directly, by enhancing or diminishing the propagation of nociceptive signals, and indirectly, by influencing affective and cognitive processes that affect the expectation, interpretation and experience of nociceptive signals (Jarcho et al., 2012). However, to date, the exact role of DA in anti-nociception and pain perception remains essentially unknown. Prior research has evidenced a dysfunction of the central DA system in chronic pain patients, including higher DA D2 receptor availability in patients with neuropathic pain and reduced presynaptic D2 receptor availability in patients with FMS (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003; Wood, Patterson, et al., 2007).

Thus, the aim of this study was to investigate the modulation of pain perception by DA in FMS patients compared to healthy controls using the [^{11}C] raclopride PET method. A second aim was to investigate whether the DA response to rewarding stimuli could

differentiate between FMS patients with and without co-morbid depression in order to better understand the depressive symptoms often associated with FMS.

This thesis focuses on two reports referring to DA activity, pain perception and reward processes in patients with FMS. In the first report, basic DA D2/D3 receptor availability and subjective ratings of pain related to the administration of painful thermal stimulation were explored in order to examine whether FMS patients would differ in D2/D3 receptor availability and its association with individual pain perception from healthy subjects. The second report aimed at investigating endogenous DA release associated with unpredictable monetary rewards to examine whether FMS patients with and without depression differ on their DA response to unpredictable reward.

The findings of each individual report have been discussed in the specific discussion section of the relevant report. In the following, the findings are briefly summarized and discussed in greater detail to disclose their implications for the role of DA in pain perception and reward processes in FMS. Furthermore, methodological issues and limitations of the study will be discussed, followed by the clinical relevance of our findings and a consideration of future research steps.

Summary of results

While the first study of this thesis examined striatal D2 receptor availability at rest and associations between D2 receptor availability and individual pain perception, the second study investigated striatal DA transmission in response to unpredictable rewards.

Report 1: Relation of Dopamine Receptor 2 Binding to Pain Perception in Female Fibromyalgia Patients with and without Depression – a [¹¹C] raclopride PET-study

Given that DA has been hypothesized to have a role in pain perception, specifically anti-nociception, we were particularly interested in the striatal D2/D3 receptor availability of FMS patients and its associations with individual pain perception. Therefore, 17 healthy controls and 24 FMS patients (11 with co-morbid MDD) underwent a PET [¹¹C] raclopride scan to determine D2/D3 receptor availability at rest. We expected FMS patients to show reduced [¹¹C] raclopride binding in striatal regions compared to healthy controls, reflecting a decreased postsynaptic availability of D2/D3 receptors in these patients. We expected the reduction to be more pronounced in FMS patients with co-morbid MDD than in FMS patients without MDD. Additionally, we aimed to test the association between pain sensitivity and striatal D2/D3 receptor binding with regard to the role of comorbid MDD. Outside the scanner, subjects were asked to rate painful heat stimuli applied cutaneously on their right volar forearm with a contact thermode. Pain thresholds, ratings of pain intensity during and after painful stimulation were recorded. Individual response characteristics to pain were determined using components from the Signal Detection Theory (Clark, 1966). We compared the discriminative capacity, i.e. the individual's capacity to discriminate between lower and higher pain intensities, and the response criterion, i.e. the subject's tendency to report pain during noxious stimulation due to psychological factors.

Unexpectedly, we did not find any differences in D2/D3 receptor availability at rest between FMS patients with and without co-morbid depression and healthy controls. Our findings are at odds with an evaluation of dopaminergic function in FMS patients using 6-¹⁸F fluoro-L-DOPA PET which revealed reduced presynaptic DA synthesis as indicated by

reduced fDOPA uptake in several pain-related brain regions, including the thalamus, mesencephalon, insula, ACC and hippocampus (Wood, Patterson, et al., 2007).

It is possible that these previous findings were influenced by methodological differences, i.e. pre-synaptic versus post-synaptic measures could explain these contradictory results. Furthermore, the reductions in 6-¹⁸F fluoro-L-DOPA uptake were limited to mesencephalon including VTA and substantia nigra, suggesting that presynaptic neuronal integrity in the mesencephalon is a more sensitive indicator of FMS than postsynaptic receptor sites. Moreover, these studies included smaller samples of patients and did not control for depression or other co-morbid disorders. Additionally, lower raclopride BP in FMS patients than healthy controls in all functional sub-regions of the striatum during non-painful saline infusion have been reported (Wood, 2008). However, it is not entirely clear if this result reflects decreased DA receptor density or a greater release of DA in response to non-painful saline infusion and is therefore not directly comparable to our experimental paradigm. No other study so far has addressed DA changes at the post-synaptic level in FMS (i.e. in the absence of noxious stimuli).

The results from the correlational analysis between D2/D3 receptor availability and psychophysical results suggest a potential link between D2/D3 receptor availability and pain perception due to psychological factors in FMS which differ however between patients with and without co-morbid depression corresponding with the assumption of an involvement of emotional and psychological processes (Geisser et al., 2003; Staud, 2004) and affect (Staud, 2004; Staud et al., 2003) in the promotion of pain in these patients. Additionally, our psychophysical results (thermal pain threshold, response criterion) support the idea of a more pronounced deficit in pain inhibition in FMS with co-morbid depressive symptoms, suggesting that depression could influence pain perception in FMS via DA.

Report 2: Increased dopamine release to unpredictable rewards in female Fibromyalgia patients with comorbid depression - a [^{11}C] raclopride bolus plus infusion PET study

In the second report, we investigated endogenous DA release associated with unpredictable monetary rewards during B/I [^{11}C] raclopride PET scanning using a validated reward task (Martin-Soelch et al., 2011) in FMS patients with and without co-morbid MDD and healthy controls to investigate if FMS is associated with dysfunctions of the central reward system. We postulated that the healthy controls would evidence an increase of striatal DA transmission in response to unpredictable reward and that this increase would be reduced in FMS patients. Furthermore, we expected FMS patients with co-morbid MDD to show a stronger reduction of this effect than FMS patients without co-morbid MDD. Surprisingly, we found a greater percentage of displacement of [^{11}C] raclopride in the right nucleus accumbens by endogenously released DA in FMS patients with co-morbid MDD compared to healthy controls. Moreover, FMS patients with co-morbid depression showed greater reductions in [^{11}C] raclopride binding in the reward vs. sensorimotor control condition in the right nucleus caudate compared to FMS patients without depression. Overall, considering the entire FMS group, we found greater reductions in [^{11}C] raclopride binding in the reward vs. sensorimotor control condition in the right nucleus accumbens in FMS patients compared to healthy controls. Furthermore, when comparing FMS patients with MDD and MDD patients, studies with MDD patients showed markedly different responses to monetary rewards, with the majority in these studies indicating hypoactivity in the ventral striatum (Diener et al., 2012; Greening, Osuch, Williamson, & Mitchell, 2014). Reasons for hyperactive DA reaction in FMS patients are very speculative and could involve an intrinsic hyper-reactivity of midbrain DA neurons (i.e. heightened phasic midbrain DA neuron burst firing to potentially rewarding stimuli) or to diminished regulatory control of nucleus accumbens dopaminergic function

stemming from a more widespread failure of inhibitory mechanisms (e.g. dysregulation of inhibitory afferents to the VTA) or due to an upregulation of the mesolimbic DA system stemming from an underactivation of striatal and prefrontal DA projections in the mesolimbic DA system. However, conclusive statements cannot be made at this point as our study did not include any DA pharmacological manipulation. Taken together, these results suggest that unpredictable monetary rewards elicit an increased DA reaction in FMS patients being indicative for dysfunctional reward processing in FMS and that dysfunctional reward circuitry could be associated with co-morbid depression in the pathology of FMS. This is the first study identifying differences in endogenous DA release during unpredictable monetary rewards in FMS patients with and without co-morbid depression and age- and gender matched healthy subjects. Our findings extend previous research on impairments of chronic pain in several aspects of reward processing (Becker et al., 2012) and suggest that FMS patients with co-morbid MDD may be distinguished from healthy subjects and that depression may reinforce this effect.

Methodological considerations and limitations

There are a few methodological issues worth mentioning: first, the results in Report 1 did not allow for differentiation between D2/D3 receptor density or intrasynaptic DA concentration and the interpretation of underlying neuronal factors should be treated with caution. Prior work indicates that [^{11}C] raclopride values from the bolus method are almost identical to binding values generated by a bolus-infusion method, in which DA release can be indirectly measured for the same subjects (Carson et al., 1997; Watabe et al., 2000). Secondly, although SPM analysis of PET ligand studies is a viable alternative to ROI analysis, especially for the exploration of changes without a priori region definitions, requirements of the analysis include transformation of the PET data to standard anatomical space, smoothing

of the data and quantitative normalization to account for global effects. In a small cohort as in our study, these processes may reduce the sensitivity to subtle changes in raclopride binding. Standardization of the basal ganglia anatomy for SPM analysis is a known challenge (in comparison to cortical anatomy). Therefore, our individual anatomy MR-based VOI analysis may be considered as better accounting for individual basal ganglia anatomy and improving the sensitivity of our PET measurements. Further, it could be argued that the painful stimuli should directly be administered in the scanner to directly determine the link of D2/D2 receptor availability with individual pain perception. However, correlating subjective ratings outside the scanner with PET measures is a standard method in PET designs in general and in the investigation of pain modulation with PET in particular (Hagelberg et al., 2002; Pertovaara et al., 2004). Finally, DA receptor binding results as well as individual responses to pain may have been biased by the participant's medication, which possibly influenced the testing procedures, including slower reaction times and anti-nociceptive effects of antidepressants. Nevertheless, we found significant differences between FMS patients and healthy subjects with regard to the estimation of pain thresholds, and a previous study found no significant group difference concerning SSRI medication regarding all pain thresholds (Klaunenberg et al., 2008). Furthermore, this aspect might also affect the findings in Report 2. Recent evidence suggests that SSRIs can reduce striatal activation under reward conditions, whereas drugs that impact the norepinephrine system accentuate this response (McCabe et al., 2010). While inclusion of those taking concomitant medications might complicate interpretation of results, one could counter that by so doing it was possible to enroll individuals with more severe FMS symptoms. Moreover, the phase of the menstrual cycle was not fixed and we did not evaluate differential aspects of distinct menstrual phases on reward-induced DA release. However, 28 of the participants were post-menopausal. Finally, as the PET [^{11}C] raclopride B/I approach permits imaging in only two conditions per scan

session, we did not measure BP_{ND} in a resting state. Thus the effect of condition observed in our analysis is specific to the reward condition vs. the sensorimotor control condition. Another limitation of this line of research is that we used responses to monetary rewards. Future research is needed to delineate linkages between laboratory measures of reward processing and real life experiences of incentive motivation, positive affect, and reward-seeking.

General discussion of the results

These data implicate DA as an important neurochemical moderator of differences in individual pain perception in FMS patients with and without co-morbid depression, and demonstrate enhanced functional engagement of the mesolimbic DA system in response to reward. The findings observed in these two reports are consistent with several lines of evidence supporting a role for disturbed dopaminergic neurotransmission contributing to clinical pain in various chronic pain conditions including FMS (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg et al., 2004; Wood, Patterson, et al., 2007). While several studies have outlined a role for DA in nociception, the precise role of DA in human pain processing has not been completely understood. It has been hypothesized that DA has direct anti-nociceptive effects (Jarcho et al., 2012; Potvin et al., 2009; Wood, 2008), however recent studies suggest a modulating role of DA in pain perception. It has been suggested that DA modulates the salience of a pain stimulus and coping response (Becker et al., 2013) and also the affective component of pain. Rather than having direct anti-nociceptive effects, DA may, thus, influence the motivation to endure or avoid pain, respectively (Becker et al., 2013) thus it is feasible that this bias towards enduring or avoiding pain is subserved by a modulation of the

affective component of pain perception, while the sensory-discriminative aspect remains unaffected.

A role for DA in pain affect has been suggested by the large anatomical and functional overlap between DA rich brain areas and areas involved in the processing of pain affect (Jarcho et al., 2012; Potvin et al., 2009). The insula and ACC in particular have been shown to receive mesolimbic DA projections as well as be involved in the affective aspects of pain (Jarcho et al., 2012; Potvin et al., 2009).

Recent evidence has linked pain and reward processing in the human brain, suggesting that DA might be involved. Additionally, FMS shares a common neurobiological characteristic, namely altered functional output of striatal DA systems mediating the processing of rewards with a range of psychiatric (i.e. substance-use disorders, affective disorders, eating disorders, and obsessive compulsive disorders) neurodevelopmental disorders (i.e. schizophrenia, attention-deficit/hyperactivity disorder, autism spectrum disorders) and genetic syndromes (i.e. Fragile X syndrome, Prader-Willi Syndrome) (Dichter, Damiano, & Allen, 2012). Therefore, DA-mediated reward-system dysfunction should be considered a potential common etiologic factor in a range of conditions. Future research could be aimed at understanding linkages between those diseases and reward function.

Perspective

With the studies presented here, we were able to fill gaps in the current knowledge related to the role of DA in pain perception and reward processes in FMS. However, these findings give rise to new research questions. A lot of unanswered questions remain about how DA contributes to nociception and how chronic pain impairs reward processing, which should be addressed in future studies.

Hence, this thesis is intended to highlight initial evidence of the relevance of DA to FMS while it is still not clear exactly how DA modulates pain perception in FMS. Pharmacological challenges remain to elucidate the context of DA's role in nociception. Further studies should also take into account both healthy persons and FMS patients. Clearly future studies are needed to address other chronic pain syndromes as well (e.g. neuropathic pain syndromes) and additionally in relation to other brain circuits and neurotransmitters.

The mesolimbic DA system represents only one component of a very complex and integrated set of circuits, and although DA is clearly a crucial neurotransmitter in the reward-processing systems, there are multiple brain regions not addressed here that contribute to reward processing, including the subthalamic nucleus, ventral pallidum, and lateral habenula (McGinty et al., 2011).

[¹¹C] raclopride has only moderate affinity for D2-like DA receptors, limiting its utility to assessments of the striatum where the density of D2 receptors is high. To overcome the above mentioned restriction to study the striatum, other brain regions comprising the DA system, including cortical and limbic structures engaged in subjective experience of pain, can now be addressed by more recently developed radiotracers, such as [¹⁸F] fallpride (Woodward et al., 2009) or [¹¹C] and FLB-457 (Narendran et al., 2011), which have higher affinities for D2 receptors.

Furthermore, the vast majority of clinical research into reward-circuitry function in chronic pain is cross-sectional in nature and focused only on adults. Therefore we cannot draw any conclusions thus far about whether the dysfunctional reactions towards rewarding stimuli were pain-induced or represent a predisposition and maybe even an increased vulnerability for developing FMS. However, there might be critical periods during development when predispositions to any pain disorders might occur, and understanding the

factors that mediate these processes will be essential for treatment and the prevention of symptom onset. Therefore, longitudinal analyses are necessary to disclose causality, and examine if differences in reward circuit and therefore neurotransmission may have preceded FMS.

It remains an open question if the observed enhancement in endogenous DA release in response to monetary rewards is a characteristic of FMS or whether this enhanced DA reaction also occurs in other pain syndromes or diseases related to stress.

Regarding the clinical implications of the present findings, treatment options involving dopaminergic parameters might be considered. Dopaminergic agents represent supportive preliminary evidence for restoring DA regulation that could be therapeutically beneficial in FMS patients (Becker & Schweinhardt, 2012). The results of report 1 support the notion that psychological therapies might hold potential as a useful modality in the multidimensional treatment of fibromyalgia. Previous studies reported psychological pain management skills as efficacious in FMS with Cognitive behavioral therapy (CBT) outperforming other psychological treatments in short-term pain intensity reduction (Vlaeyen et al., 1996). Given that FMS is still difficult to treat, investigations of reward-circuitry functioning may have implications for clinical practice and open new treatment options for FMS.

The results of report 2 imply therapies such as e.g. mindfulness-based interventions such as the mindfulness based stress reduction program (MBSR) (Kabat-Zinn et al., 1998). This program widely used for the treatment of chronic pain conditions (Chiesa & Serretti, 2011) and might be a non-pharmacological treatment option restoring the functionality of the reward system as this intervention has been shown to be associated with an increased experience of momentary positive emotions as well as greater appreciation of, and enhanced

responsiveness to, pleasant daily-life activities (Geschwind et al., 2010; Segal, Vincent, & Levitt, 2002).

More recently, Mindfulness-Oriented Recovery Enhancement (MORE), a new multimodal intervention designed to address chronic pain, craving and opioid misuse behaviours integrating training in savouring natural rewards with mindfulness training has been shown to decrease pain severity and enhance natural reward processing in chronic pain patients (Garland, 2014; Garland, Froeliger, & Howard, 2014).

Furthermore, deep brain stimulation, a neurosurgical technique involving the implantation of electrodes in the brain for modulation of pathological neural activity, has been shown to normalize striatal reward function in depression and eating disorders (Pizzagalli, 2011). This method could possibly provide an opportunity to normalize the striatal reward function in FMS.

Finally, poorly defined conditions such as FMS could benefit from objectively measurable biomarkers that could be used to verify the diagnosis of FMS, identify subgroups of FMS patients or to follow disease progress. Therefore, enhancement in endogenous DA release in response to monetary rewards as observed in our FMS patients that differed between patients with and without co-morbid MDD could present a promising target.

Conclusion

Together, our data add to the mounting evidence for a disruption of normal dopaminergic neurotransmission in the pathophysiology of FMS as described by Wood and Holman (2009) "as an elephant among us waiting to be noticed as it occupies an increasing amount of floor space in the vault of our knowledge regarding FMS" (Wood & Holman,

2009). Further progress in our understanding and management of this disorder requires a better understanding of dopaminergic neurotransmission and therapeutic strategies aimed at manipulating dopaminergic parameters as a relevant approach for the treatment of this disorder.

KATHARINA LEDERMANN

Bachtobelstrasse 10

8045 Zürich

Email: katharina.ledermann@usz.ch



OBJECTIVES:

Date of birth: 1th. April, 1984

Nationality: Switzerland

CURRENT POSITION:

PhD student at the University Hospital Zurich, Department of Psychiatry and Psychotherapy
Research assistant Department of clinical psychology University Fribourg

DISSERTATION:

A [¹¹C] raclopride PET study on Dopamine activity, Pain perception and Reward processes in patients with Fibromyalgia

Advisor: Prof. Chantal Martin-Sölch, Prof. Lutz Jäncke

EDUCATION

PhD University of Zurich (Switzerland)
Structural PhD Program Psychology, 2010-present

M.A. University of Berne, Switzerland,
Neuro- and Social Psychology, 2009
Masterthesis: Gender Effects in Self-presentation, grade “summa cum laude”

University Padua (Italy),
Cognitive experimental psychology, spring term 2008 (student exchange)

B.A. University of Bern,
Psychology, 2007

PROFESSIONAL EXPERIENCE

March 2014 – Dec 2014

University hospital Zurich, department of psychiatry and psychotherapy and department of rheumatology, clinical psychologist in the Work Hardening Program for chronic pain patients

Since August 2012

University of Fribourg Switzerland, Department of clinical Psychology, research assistant

Since August 2010

University hospital Zurich, Department for psychiatry and psychotherapy in the from the Swiss Science foundation supported project

A [11C] raclopride PET study of dopamine activity, pain perception and reward processes in patients with Fibromyalgia

March 2010 - July 2010

University hospital Zurich, department for psychiatry and psychotherapy, psychologist and research assistant

Oct 2009 - Dec 2009

University hospital Zurich, Department for neurology, internship as clinical neuropsychologist

Oct 2008 – Feb 2009

Pedagogical school Berne, Switzerland
Research assistant

July 2008-Sept 2008

University Berne, Department for Neuropsychology
internship experimental psychology supervision Prof. K. Henke

CONTINUED EDUCATION

From Feb 2014

Advanced training in Cognitive Behavioral Therapy at the Academy for behavioral medicine and methodological integration (AIM), Switzerland,

March 26-30 2012

SPM8 for basic and clinical investigators, Prof. T. Zeffiro Northwestern University Chicago

2011

MRI Safety Course Dr. R. Lüscher, ETH Zurich

2011

Training in the conductance of structured clinical interviews (SCID), Dr. A. Delsignore Department of Psychiatry and Psychotherapy, University Hospital Zurich

2010

Good clinical practice training, level I&II, center for clinical research, University Hospital Zurich

Since April 2010

Participation in the colloquia of Psychotherapy and Psychosomatics, Department of Psychiatry and Psychotherapy, University Hospital Zurich, Switzerland

- 2010 PET data analysis introduction course, Imperial College London, UK
- 2009 Mindfulness based stress reduction (MBSR) course, University of Berne

TEACHING EXPERIENCE

- Spring term 2014 Psychiatric disorders and cognitive impairments in the elderly, University Fribourg, Switzerland
- Autumn term 2013 Conduite d'entretiens structurés, University of Fribourg, Switzerland
- Spring term 2013 Conduite d'entretiens structurés, University of Fribourg, Switzerland
- 2013 Supervision of 4 M.A. and 1 B.A. in the project "La douleur chronique au quotidienne" University of Fribourg
- Autumn term 2012 Psychopathologie du vieillissement: troubles cognitifs et démences University of Fribourg, Switzerland
- 2011 study modul for medical students: scientific approaches to psychiatric diseases; topic: experimental psychopathology, University of Zurich, Switzerland
- 2011 study modul for medical students: scientific approaches to psychiatric diseases; topic: "pain physiology and pain perception" University of Zurich, Switzerland

PUBLICATIONS:

Ledermann, K.; Jeanmonod, D., McAleese, S., Aufenberg, C., Opwis, K., Martin-Soelch, C. (under review at Stereotactic and Functional Neurosurgery) Effects of the cerebello-thalamic tractotomy on cognitive and emotional functioning in Essential Tremor: A case control study

Kuhn, F.P., Warnock, G., Burger, C., Ledermann, K., Martin-Soelch, C., Buck, A. Comparison of PET template-based and MRI based image processing in the qualitative analysis of C11-raclopride PET (*EJNMMI Research* 4:7)

Relation of Dopamine Receptor 2 Binding to Pain Perception in Female Fibromyalgia Patients with and without Depression – an [¹¹C] raclopride PET Study
Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Warnock, G., Johayem, A., Kollias, S., Buck, A., Martin-Soelch, C., (under review at Neuropsychopharmacology)

Increased dopamine release to unpredictable rewards in female Fibromyalgia patients with comorbid depression - a [¹¹C] raclopride bolus plus infusion PET study
Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Warnock, G., Johayem, A., Kollias, S., Buck, A., Martin-Soelch, C., (under review at JAMA)

Selecting portraits for self-presentation in social media: Why men prefer facial prominence more than women

Sczesny, S., Kaufmann, M., Ledermann, K. (under review at Journal of Personality and Social Psychology: Personality Processes and Individual Differences)

POSTER PRESENTATIONS:

Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Burger, C., Johayem, A., Cservednyak, T., Kollias, S., Buck, A. Martin-Soelch, C. *Reduced striatal D2 receptor binding in Fibromyalgia*. in *8th IBRO World Congress of Neuroscience*. 2011. Florence, Italy.

Martin-Soelch, C., Ledermann, K., Jenewein, J., Hasler, G., Schnyder, U., Burger, C., Johayem, A., Cservednyak, T., Kollias, A., Buck, A., Sprott, H. *Is Fibromyalgia a neuropathic pain disease?* . in *7th Congress of the European Federation of IASP® Chapters (EFIC)*. 2011. Hamburg, Germany. European Journal of pain Supplement Volume 5 Number 1 September 2011 ISSN: 1754-3207

POSTER SESSIONS/ European Journal of Pain Supplements 5 (2011) 15-295 auf Seite 231

Martin-Soelch et al. The role of Dopamine in pleasure and pain: a 11C-raclopride bolus plus constant infusion PET study of unpredictable monetary rewards in chronic pain. Abstract presented at the Fribourg Day of Cognition, Center for Cognition, Fribourg, 12th september 2012.

Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Burger, C., Johayem, A., Cservednyak, T., Kollias, S., Buck, A. Martin-Soelch, C.

Differences in Dopaminergic Response to unpredictable Rewards in the right Ventral Striatum in Fibromyalgia patients: A 11-C raclopride Bolus Plus Constant Infusion PET study. In *Annual meeting of Society for Neuroscience*, New Orleans (USA), 13.-17. October 2012.

Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Burger, C., Johayem, A., Cservednyak, T., Kollias, S., Buck, A. Martin-Soelch, C. *Differences in dopaminergic response to unpredictable rewards in Fibromyalgia patients with and without co-morbid depression: a 11-C raclopride bolus plus constant infusion PET study* in Swiss Psychological Society congress, Basel, 11. and 12. September 2013

Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Burger, C., Johayem, A., Cservednyak, T., Kollias, S., Buck, A. Martin-Soelch, C. *Differences in striatal D2 receptor availability and pain modulation related to depression in Fibromyalgia – a [11C] raclopride PET study* in *8th Congress of the European Federation of IASP® Chapters (EFIC)*. 2013. Florence, Italy.

Ledermann, K., Jenewein, J., Sprott, H., Hasler, G., Schnyder, U., Burger, C., Johayem, A., Cservednyak, T., Kollias, S., Buck, A. Martin-Soelch, C. A common neurobiology for reward, chronic pain and depression? A [11C]raclopride bolus plus constant infusion PET-study European Neuropsychopharmacology (Impact Factor: 4.05). 10/2013; 23(2):354.

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